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THE

# AMERICAN JOURNAL

# OF THE MEDICAL SCIENCES

JUNE, 1929

## ORIGINAL ARTICLES.

### CHRONIC APPENDICITIS.*

By John B. Deaver, M.D.,

SURGEON IN CHIEF, LANKENAU HOSPITAL, PHILADELPHIA, PA.

My reason for speaking upon chronic appendicitis is because of what I believe to be unwarranted statements that chronic appendicitis is not a clinical entity, statements that are being made by those whose observations on the living subject at operation are not sufficiently large to warrant such pronouncements. I hope to show the fallacies of these statements. There is no doubt but that many deaths result from an acute exacerbation supervening upon a chronically diseased appendix, which naturally is more vulnerable than the normal appendix, so that loss of life may often be the price the patient pays for this erroneous attitude.

At the outset, it must be admitted that the first and most important step in the handling of any morbid condition is the diagnosis. Diagnosticians of today are of three classes, the clinician, the radiologic-clinician and the radiologist. The first acquires experience and judgment by time and labor spent in the study of pathology and from a large practice in which he has seen and treated all types of disease. This fortunate doctor is of much value to his clientele, especially if he has been tutored by a Master, and has the prerequisites of good common sense and the ability to use the special senses with which nature has endowed him.

The radiologic-clinician is he who depends as much, if not more, upon the radiologic than upon the clinical findings, with a consequent weakening of his own confidence. I feel it is because of this that the average medical man or the average surgeon of today is not as

* Read before the Inter-State Post-Graduate Association of North America, Atlanta, Ga., October 15, 1928.

good a diagnostician as in former times. Too many doctors are unwilling to venture an opinion in the chronic abdominal case without a roentgenogram. In fact, the laity now know so much, or rather so little, about the picture business that they demand this form of examination. My answer to this request is, "I am not yet a picture doctor." The radiologist is the third type of diagnostician who studies the case from its roentgenologic manifestations but familiarizes himself with the history of the case before he gives his report.

However this may be, there are certain points that every diagnostician must bear in mind. The appendix is a diverticulum, an offshoot of the alimentary canal, with a like anatomy, histology and physiology, and with a vascular supply out of proportion to its size. The mucous membrane is ciliated with the cilia directed toward the outlet and the arrangement of the muscular coat such as to favor contraction in the same direction. This arrangement of the anatomy enables the appendix to empty when its lumen does not contain foreign matter, such as fecal concretions, and when the coats are infiltrated by products of inflammation. The valve of Gerlach at its outlet prevents regurgitation of the cecal contents only under normal conditions. Unsuccessful efforts of the appendix to empty cause appendiceal colic, therefore, as appendicitis is primarily the result of disturbed anatomy which necessarily affects the physiology. The physiology of the appendix was carefully considered and proven long ago by the famous Scotch surgeon, Sir William MacEwen whose deductions were always logical. MacEwen reached his conclusion by a study of the cecal secretions obtained through a fistulous opening in the cecum close to the appendiceal opening, and concluded that the appendix plays a part in cecal digestion and that the cecum and the appendix play an important part in the final stages of intestinal digestion. Practically, therefore, the physiology of the appendix plays a rôle in the pathology of inflammation of the appendix. Furthermore, recent studies show that a connection exists between the appendix and the ileocecal muscle, demonstrable by electric stimulation; also that the appendix is part of the cecal apparatus, that is to say, a lymphatic portion of the intestine with an accessory digestive action, and finally, the mutual influence of the lymph follicles of the gastrointestinal tract, as evidenced by its action in producing changes in the ingesta, seems to regulate intestinal activity in general just as the appendix does in its own region. One of the functions of lymph follicles, as we all know, is to prevent inflammation. Thus the appendix also has a physiologic function, and serious interference with the function of the cecum and the appendix may give rise to disease. This is instanced by the fact that the majority of cases of appendicitis are associated with the digestive process. Disturbed cecal and appendiceal digestion has an effect upon the small intestine and the latter in turn upon the

cecum and the appendix. Irritation and inflammatory changes in the appendix, through the superior sympathetic mesenteric plexus, produces pain in the abdomen and especially in the region of the umbilicus and of the epigastrium. This is what causes confusion in the early localization of the lesion and gives rise to the belief that the patient is suffering from gastric indigestion or a disturbance in the upper part of the lower intestine.

The nerve supply of the appendix is through the superior mesenteric plexus, the branches of which go to the appendix accompanying the ileocolic artery. The usual site of pain in chronic appendicitis is at McBurney's point and is the result of reflex action. Irritation of the appendix is reflected back to the plexus which is related by branches to that part of the spinal cord giving off the lower dorsal and upper lumbar nerves. Sherren states that this reflex pain occurs oftenest in the area of distribution of the eleventh dorsal nerve. Pain may thus be referred to the right thigh, the right testicle or the right lumbar region. Referred pain in appendicitis often confuses the situation, no better example of which is the confusion of the pain of appendicitis with neuralgia of the lower intercostal nerves.

Disturbed cecal and appendiceal digestion results in lack of proper secretion of the succus entericus and lowering of the activity of the lymph nodes, causing loss of control of the bacteria that swarm the cavity of the cecum and the appendix. Although in pathologic conditions the colon bacillus is the surgeon's arch enemy, in its proper place it serves a useful purpose in effecting the disintegration of undigested matter, but when the organs are unhealthy it leads to the production of toxins. In cecal appendiceal indigestion, stasis and constipation occur on account of the abnormal amount of succus entericus. Fermentative changes take place in the cecum and the appendix which with absorption of toxins causes the diarrhea met with in some instances. Disturbed cecal and appendiceal digestion, in the presence of pus organisms, produces sequelæ that have a serious effect on the appendix resulting in chronic disease.

Indigestion causing discomfort in the alimentary tract is a very vague and loosely employed term. The appendix and cecum having a rich supply of glands of Lieberkühn, they both play a part in digestion. Appendiceal indigestion or dyspepsia is therefore the proper term, since interference with the digestive function of the appendix and the cecum will, as a matter of course, sooner or later give rise to disease ending in a chronically diseased appendix. If we remember that the glands of Lieberkühn are by far more numerous and better developed in the ascending colon, the cecum and the appendix than in the small intestine, we shall appreciate the import of cecal and appendiceal digestion.

McEwen clearly states that in most appendices removed at operation one sees that the surface is covered with the glands of Lieber-

kühn in an active state of secretion, during health, thus making the secretion of the appendix alone a valuable aid to digestion.

Chronic appendicitis is seen as a catarrhal or interstitial or obliterative (appendicitis obliterans) type, the last being the terminal stage of the interstitial. In its gross as well as its microscopic pathology the chronically diseased appendix very much resembles the chronically diseased gall bladder, even to enlargement of the lymph nodes at the base of the appendix, within the mesoappendix and the mesocecum or mesocolon, corresponding to enlargement of the cystic node at the neck of the gall bladder and the nodes along the common duct; the nodes in both conditions show microörganisms, and thus emphasize the danger of extension of infection by way of the lymph vessels. In the diseased appendix, as in the diseased gall bladder, infection is also carried by way of the tributary veins of the portal system of which the appendicular veins are a part. Bacteriologic study of the nodes in relation with the diseased appendix shows the hemolytic streptococcus in about 50 per cent of the cases. (Research Laboratory, Lankenau Hospital.)

Chronic appendicitis is as much an entity as chronic peptic ulcer or chronic cholecystitis. Those who cry loudest against this entity I fear form their opinions, in many instances, from deductions made from their study of the outside of the abdomen. Chronic appendicitis cannot always be diagnosed by the radiologic-clinician or the radiologist since not all chronic appendices retain bismuth or barium, for example, the interstitial type if at all advanced, or if it contains concretions, and the chronic catarrhal type whose lumen is often obstructed by concretions or by stricture. To make the diagnosis of chronic appendicitis dependent upon Roentgen ray findings is a delusion and a snare. Clinical experience and clinical diagnosis still count and mechanical diagnosis will not and cannot win over clinical diagnosis. While this may be the age of machine power over man power, the art of diagnosis still rests upon human power.

Chronic appendicitis frequently comes on insidiously, without pain, but with more or less indigestion and abdominal discomfort. Not all chronic appendices are the result of a previous acute attack, but may be due to a low-grade intestinal infection. Chronic appendicitis the result of a previous acute attack or attacks is followed by intermittent attacks of mild pain, epigastric distress, due to reflex pylorospasm, occasional nausea and more or less gaseous distention particularly of the small intestine, a syndrome that at times is impossible to differentiate from a mild chronic cholecystitis or a typical duodenal ulcer or a mild chronic pancreatitis. It is in this type that palpation will elicit rigidity of the overlying abdominal muscles, tenderness and oftentimes an enlarged appendix. The second type is that in which the symptoms appear insidiously with indigestion,

slight abdominal discomfort, and mild intestinal distention, where violent exercise or fatigue causes lower right abdominal discomfort and not infrequently, pain. Here gentle palpation by skillful touch will reveal characteristic findings: some loss of flexibility of the overlying abdominal muscles, tenderness and not infrequently a palpable appendix. The palpable appendix must not be mistaken for the wall of the cecum, especially if it contains soft feces, the semilunar line, or the lateral border of the rectus muscle. The stumbling point in making the diagnosis by palpation is that many a doctor practises medicine a lifetime and never acquires the sense of touch. Touch, I consider, the greatest asset in making the physical examination, and in the case of the diseased appendix it is far superior to any Roentgen ray examination. Gentle touch, skillful touch, refined touch make for much more in the diagnosis than the heavy hand or the Roentgen ray can accomplish.

The diseased appendix, like the diseased gall bladder and the diseased duodenum causing pylorospasm, causes a spasm of the muscle fibers of the ileocecal junction and leads to lower right abdominal discomfort. The chronically diseased appendix causes referred pain, the point of reference depending upon the position of the appendix and the direction in which it points. In the diagnosis, not only of chronic but of acute appendicitis as well, the position of the appendix and the direction it assumes have a most important bearing.

The most common positions of the appendix, as I have frequently pointed out, are lateral to and behind the cecum and colon, in the pelvis, beneath the terminal ileum and mesentery and pointing downward and backward to the left, above the terminal ileum and mesentery pointing upward and to the left, to the mesial side of the cecum and colon and anterior to the cecum and colon. I see a number of cases where pain is referred to a point immediately above Poupart's ligament on the right side and where a diagnosis of commencing hernia, on account of what is believed to be succussion on coughing, is made. These patients are tender to pressure over the area of referred pain with loss of normal flexibility of the overlying muscles as compared with the opposite side, and upon careful examination do not present any definite signs of hernia. At operation, the appendix is found inflamed while the inguinal canal is found normal. On the other hand, the two conditions are occasionally combined. It is the practice in the Lankenau Clinic, when possible, to remove the appendix through the hernial wound when operating for right inguinal hernia. This is practical in all but a few cases. The exceptions are where the cecum holds a high position and cannot be brought into the wound and where the appendix is retrocecal or retrocolic and adherent, or is in one or another of the possible positions making it inaccessible to attack through the

inguinal canal. In such circumstances, the appendix should be removed through a second incision. In practically all these cases the appendix is found diseased.

In removing the appendix through the hernial wound, great care is needed in tying off the mesoappendix, seeing that it is relaxed not tense, when the ligature or ligatures are applied, otherwise bleeding may occur after the cecum has been replaced. Furthermore, if the appendiceal stump is not thoroughly sterilized, contact with adjacent tissues may result in infection, defeating the object of the operation —the cure of the hernia. The only sure method of sterilization is amputation with the cautery at a white heat. If the appendix is diseased, as is usually the case, and one cannot be sure of his technique, it is better to make the usual appendiceal approach, than to attempt to take it out through the hernial wound.

Our experience in incidentally finding a chronically diseased appendix while operating for other conditions has convinced us beyond any question of doubt of the soundness of the statement that chronic appendicitis is not only an entity but an enemy as well to its possessor.

It will be seen how confusion may occur if the pain is referred elsewhere than to the neighborhood of the cecum. For example, where the appendix is located in the pelvis the pain is referred to the lower left abdomen. Furthermore, especially in children, if the cecum has not completely descended, doubt may be injected into the question.

Many of our operations include not only the removal of a chronically diseased appendix left at a previous abdominal operation, but also operation for acute attacks including all varieties, many of which are admitted with a lethal peritonitis. With few exceptions, not removing the appendix in all abdominal operations, especially of the lower abdomen, I know has been the cause of many a fatality in a subsequent attack of acute appendicitis. In the hands of the skilled operator, this little additional piece of work adds no risk. We should remember that to relieve pain and prevent death are our two chief missions. We are all familiar with the condition of acidosis most often seen in children, many of whom suffer repeated attacks. A deranged alimentary canal is most often the cause, so that taking out the chronically diseased appendix is the logical thing to do as a preventive. This is made clear by what I have said in describing the function of the appendix. Many of you are constantly advising removal of the tonsils and teeth for otherwise indeterminable conditions, but you are not advising removal of the chronically infected appendix, which I believe to be indirectly responsible for more deaths than all of the above combined.

The conditions most commonly confused with or mistaken for chronic appendicitis are chronic peptic ulcer, chronic cholecystitis,

a mobile splashing and tender cecum with or without coloptosis or visceroptosis, and stone in the right ureter. Other conditions are carcinoma of the cecum, tuberculosis of the cecum, tuberculosis of the peritoneum, of the lymph node at the junction of the ileum and the cecum, diverticulosis, chronic diverticulitis, retroperitoneal lymphangitis, effusion within the psoas sheath, early psoas abscess, chronic right-sided pyelitis, stricture of the right ureter, stone in the ureter, and a chronic lesion of the right uterine appendage. Of these various conditions, with the exception of carcinoma or tuberculosis of the cecum, the ones most frequently encountered are pyelitis and chronic disease of the right uterine appendage. In early carcinoma and tuberculosis of the cecum, before there is a definitely palpable mass, the differentiation can only be made with certainty, by incision, inspection and touch; therefore, when in doubt, operate. Where there is a small palpable mass, I rarely have a Roentgen ray examination made fearing it will not be correctly interpreted and that operation will be deferred, resulting in the disaster of delay. Better operate and find nothing than operate and find too much, is a dictum that bears endless repetition. Multiplicity of consultations and of roentgenograms have, in many instances, taken away the advantage of early operation. Opening the abdomen in order to dispel doubt and reveal truth is certainly attended by less risk than waiting for a hair-splitting diagnosis, to decide the question. In this age of mechanical and laboratory diagnosis, the surgeon's hand is too often stayed by consultants who shoot at, but too often miss the bull's eye. In early carcinoma of the right colon or tuberculosis of the cecum, before there is metastasis, operation is curative while delay robs the patient of the chance of cure. I cannot stress this too strongly, for at the present day not to take out a chronically diseased or a doubtful appendix is exposing the patient to unjustifiable risks. Even if all the symptoms of which the patient complains are not cleared away by removal of the appendix, the patient's assurance against future acute attacks, metastatic infection and death more than warrants the interference. I am free to confess I am not in sympathy with my colleagues who oppose this stand.

It is taken for granted that the surgeon who removes the chronically diseased appendix must be competent to excise the terminal ileum, the cecum and ascending colon should the case prove to be carcinoma or tuberculosis of the cecum, or carcinoma of the colon. I fear that the operation of taking out the appendix is thought to be so simple that it frequently is done by one not capable of handling a more serious condition. However, this is not an argument against what I am pleading for.

Pyelitis, as well as stricture of the ureter and ureteral stone, can, be differentiated from appendicitis by a careful physical examination, chemical study of the urine, by cystoscopy, Roentgen ray,

pyelography and uretography. When, as often happens, the two conditions, stone in the ureter and chronic appendicitis, are present the appendix can be taken out through the incision for exposing the ureter, which should be an extraperitoneal one.

In case of confusion between chronic appendicitis and chronic disease of the right uterine appendage, the history of vaginal discharge together with vaginal and rectal examination will usually suffice to make the differentiation.

Differentiation between a chronic noncalculous cholecystitis and a chronically diseased high-lying appendix is oftentimes difficult and occasionally impossible, nor does cholecystography always help us. It is my experience that if careful study of the history with painstaking physical examination does not make the diagnosis, it will usually not be made by Roentgen ray study.

Gall-bladder indigestion, in contrast with the indigestion of chronic appendicitis, presents characteristic symptoms such as discomfort, nausea, belching of gas soon after eating, and in the more aggravated cases, vomiting. Thus one can often make a differential diagnosis from the history alone. It is well known that greasy and highly-seasoned food aggravates the gall-bladder patient, while this is not necessarily true of the appendiceal patient. Careful consideration of these and other points brought out in the history will act as guides in reaching a correct conclusion. I often wonder whether, with our present-day accomplishments, we are not neglecting the old and valuable methods in diagnosis.

Next to the history, the physical examination is of greatest diagnostic importance especially in the presence of a mass or of definite rigidity and tenderness. In the physical examination, sight and touch play the chief rôles. In both acute and chronic disease of the abdomen, by having the patient lie perfectly flat upon the back, and by observing the contour of the anterior abdominal walls during normal and forced breathing, much information is obtained, such as irregularities, increased pain caused by deep breathing, and the absence of movement of part of or of the entire abdominal wall.

In the differentiation between chronic noncalculous cholecystitis and a high-lying chronic and tender appendix, when the patient gives a typical history, palpation, if properly made, usually will help to locate the pathology. In the enlarged chronically diseased gall bladder palpation detects a swelling movable with respiration which, with tenderness and overlying rigidity makes the diagnosis comparatively certain. In the absence of a palpable gall bladder, light pressure over the normal site of the fundus, that is to the right of the border of the rectus muscle, and immediately below the junction of the ninth costal cartilage and rib will elicit rigidity and tenderness, their degree depending upon the degree of the gall-bladder inflammation. With the fundus brought in contact with the abdominal wall, having

the patient breathe deeply and hold his breath, finger pressure will increase the pain. I attach much importance to demonstrating the site of pressure pain in the differentiation between gall-bladder and appendiceal disease.

In the tender high-lying appendix, the tenderness can be traced from below upward, the tender area corresponding to the position of the appendix. In addition to the appendiceal tenderness, the enlarged appendix can often be palpated.

Cholecystography and Roentgen ray examination have not given me as much satisfaction in differentiating between the chronic gall bladder and the chronic appendix, as have a carefully taken history and a carefully conducted physical examination. The latter I consider paramount in the diagnostic study of surgical abdominal ailments. Roentgen ray examination in the diagnosis of chronic appendicitis has never appealed to me since the Roentgen ray report stresses the presence of tenderness in the manipulations in carrying out the examination, much if not more, than retention of a part of the barium meal.

In the female, the symptoms are, not uncommonly, more marked at the menstrual period. More important than the symptoms, however, are the physical findings, such as tenderness over the location of the appendix, with a certain degree of rigidity or stiffness of the overlying abdominal walls. To elicit these signs requires skillful touch born of large experience in abdominal diseases.

That the chronic appendix is a menace is evidenced by the fact that it is found diseased in practically all cases of abdominal disorders such as chronic cholecystitis, and chronic peptic ulcer, so that it undoubtedly is a factor in the etiology of these conditions. In the cases where the appendix has been taken out, it is altogether possible that it was the original focus of infection, for it must be admitted that the appendix is the most common site of intra-abdominal infection, so that it is a common site from which infection migrates.

It is not an uncommon experience in badly infected appendiceal cases to have the kidneys involved, as evidenced by hyalin and granular casts, albumin, and so forth, in the urine, and to find that in most of these cases when the appendiceal infection has been eradicated the kidney condition clears up; also where the infection has lasted a long time the kidneys have become permanently damaged. Assuming this to be so, does not the infected appendix play a rôle in the etiology of Bright's disease? In my opinion, this is as likely as that neglected scarlet fever leads to chronic nephritis.

I believe that many cases, where a chronically diseased appendix is responsible for the abdominal discomfort, are now being treated for indigestion, dyspepsia, mild colitis and intercostal neuralgia, and so forth. The history of the case with careful physical examination

and a knowledge of the many conditions that can simulate a chronically diseased appendix will solve the riddle in nearly all such instances. I am daily demonstrating this in the Lankenau Clinic, in the study of the pathology of the living. Medication and colonic lavage will not cure the chronically diseased appendix any more than medical drainage of the gall bladder will cure chronic gall-stone disease. The money misspent in Roentgen ray examinations and laboratory investigations in the study of abdominal ailments is appalling, and the results disappointing, to say the least. I have these studies made only where the patient's history is not clear and the physical examination is negative.

I classify all cases of appendicitis as either acute or chronic. The acute includes the catarrhal, interstitial, subacute, relapsing, perforative, gangrenous and phlegmonous types. In any or all of these varieties, there are constitutional symptoms, pain, nausea or vomiting or both, increased pulse, temperature and leukocytosis; also abdominal rigidity, tenderness and often a palpable mass.

To differentiate these types of the acute appendix is not always possible and the attempt to do so only complicates the situation. The two words, acute appendicitis, include all the types, and hair-splitting diagnosis often does not get the patient anywhere, except perhaps, to the grave. So with chronic appendicitis, the clinician who can differentiate the various types has not yet been born. There are clinicians, however, who impress their patients with their ability to differentiate between a terminal neuritis of the lower intercostal and iliohypogastric nerve and chronic appendicitis, and are bold enough to declare that pain in the lower right abdominal quadrant is more often the result of such, than of a chronically diseased appendix. This declaration will, I am sure, be the cause of many deaths from acute attacks superimposed upon a chronic appendicitis.

The fact that all patients who are operated upon for chronic appendicitis are not relieved of all of their symptoms does not prove that there is no such entity. I challenge my opponents to prove their claim by specimens from the living subject, and to show that lurking infection in the appendix is not responsible for some, if not most, of the upper abdominal conditions which the surgeon is constantly revealing at the operating table.

I do not deny the rôle of other sources of focal infection, such as the tonsils, the teeth and the sinuses, and so forth, but I do claim that compared with the appendix their rôle is an inconspicuous one, otherwise we surgeons would not find upper abdominal inflammation and appendiceal inflammation associated in practically all cases. At least, I may say, that this has been my experience in the many thousand abdominal operations that I have performed.

# CHRONIC BRONCHIECTASIS IN CHILDHOOD, WITH OBSERVATIONS ON EARLY DIAGNOSIS.

By Edward S. Thorpe, Jr., M.D.,

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(From the Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia.)

Bronchiectasis, whether affecting adults or children, represents but one aspect of the composite picture of chronic, nonspecific pulmonary disease. Three types of this condition have been described in the pediatric literature: (1) A congenital form, variously reported as "congenital cystic formation of the lungs" or "atelectatic bronchiectasis," which is found rarely in stillborn children; (2) an acute type, called "bronchiolectasis" and observed in the terminal bronchioles of marasmic infants; (3) finally, that type—most commonly recognized—which occurs as the result of chronic pulmonary infection. The latter type, which is of prime importance in any study of thoracic diseases, will be dealt with in this paper. From the records of the Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia for the years 1923 to 1928, I have selected 53 cases* which I have felt demonstrated this condition in children under thirteen years of age, and these have been used as the basis for conclusions. Several additional cases have been excluded which were due to foreign bodies of long residence, though it is conceivable that they very properly might be added to this group. I have also excluded cases in which bronchiectasis complicated proven pulmonary tuberculosis.

There is a paucity of literature on the subject of bronchiectasis in children and even those articles reviewed were almost barren of references concerning its relative frequency. Vital statistics and hospital records give no clue to its incidence. Half of the cases reported here were revealed only when the histories and roentgenograms of children variously classified as chronic pneumonitis and so forth were carefully restudied. In this series 31 were males and 22 were females and death occurred in 4 cases. Willis Lemon[1] of the Mayo Clinic recently reported 63 cases of bronchiectasis in children which occurred in 15,500 admissions during a five-year period and noted 3 mortalities. Experienced observers, such as Landis,[3] or Davidson and Pearson,[2] agree that the incidence of bronchiectasis is much greater than anyone has reported to date.

* The case histories here reviewed were selected from the records of the University and Children's Hospitals. The courtesies extended by Dr. J. C. Gittings, Dr. J. P. C. Griffith, and Dr. Alfred Hand are hereby acknowledged. Dr. Henry Pancoast and Dr. Eugene Pendergrass rendered considerable aid in the selection and interpretation of roentgenograms. Dr. Chevalier Jackson and Dr. Gabriel Tucker extended the aid of the Bronchoscopic Clinic in the review of their records.

**Etiology.** The exact etiology of an essentially chronic disease such as bronchiectasis is often difficult to determine. There are so many serious infectious diseases of early childhood which may profoundly damage the respiratory tract, and they often follow one another with such surprising rapidity that more than one may be responsible for the pathologic changes in the bronchi. Bronchopneumonia seems to be the most frequent antecedent of bronchiectasis in this series, being the causative factor alone in 23 cases; however, 26 other cases gave the history of secondary attacks of pneumonia, and several of the children had suffered as many as 5 recurrences. Lemon's[1] report shows that pertussis was the most frequent precursor, occurring in 27 of his 63 cases, but in this series pertussis was the definite forerunner in only 14, although 17 additional children had contracted this disease at some time during their lives. Measles accounted for 9 cases but had occurred in 18 others, influenza incited 3 cases and 2 cases had no precursor other than repeated upper respiratory-tract infections. Diphtheria with laryngeal stenosis and six years of cannulation was responsible for 1 case, and poliomyelitis with resultant paralysis of the diaphragm, atelectasis and secondary infections for another.

However, the exact rôle of any special diseases in the causation of bronchiectasis is a matter of conjecture for the real etiologic factor is a chronic infection so deeply implanted in the bronchial walls and supporting tissues of the lung that there results stagnation of secretion, increased intrabronchial tension from cough and finally ectasis of tubes which have lost the resilience of their structural framework.

Following the report of Mullin[4] attention has been directed frequently to the apparent causal relationship between diseases of the nasal accessory sinuses and bronchiectasis. The impression gained from study of these cases and other reports is that one cannot evaluate accurately the entire significance of the upper respiratory-tract infections in the production of such an advanced pathologic entity as bronchiectasis. All but five of the children reported in this series gave histories of repeated upper respiratory infections since early infancy. In 38 there was demonstrable evidence of residual processes, such as sinusitis, pharyngitis, otitis and septic tonsils, not to mention lymphadenopathy. Thus, one must either assign the cause of bronchiectasis in almost all cases to these diseases, or one must conclude that they play a concomitant part only in the maintenance of residual infection. My conception of the natural history of bronchiectasis is that there is a common gradient of respiratory-tract pathology down which one proceeds following bronchopneumonia, a disease capable of implanting infection deep in the structures of the lung.

Given a child with rickets, undernutrition and a poor environment, and the ground is prepared for the seeds of such an infection. Various other acute febrile disorders follow rapidly, leaving in their

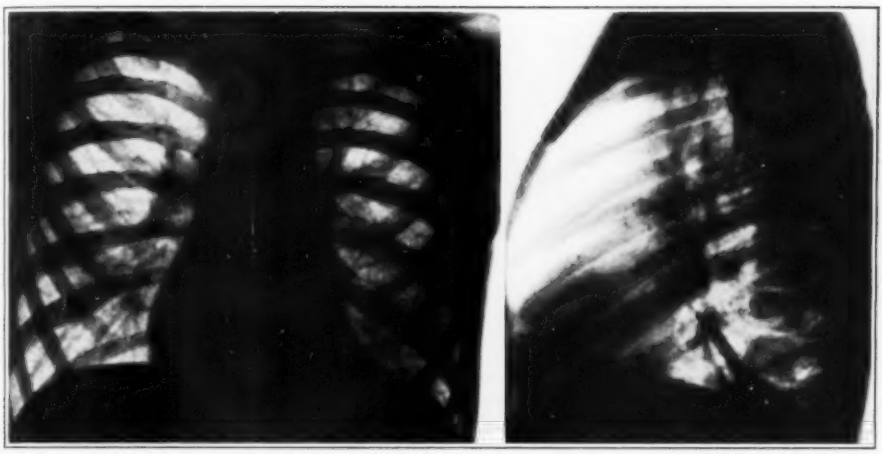


FIG. 1.—(Case I.) Roentgenograms of the anteroposterior and lateral aspects of Case I before treatment, showing moderate bronchiectasis at the right base and interlobar pleurisy. Note obliteration of the right lower angle of the cardiac outline.

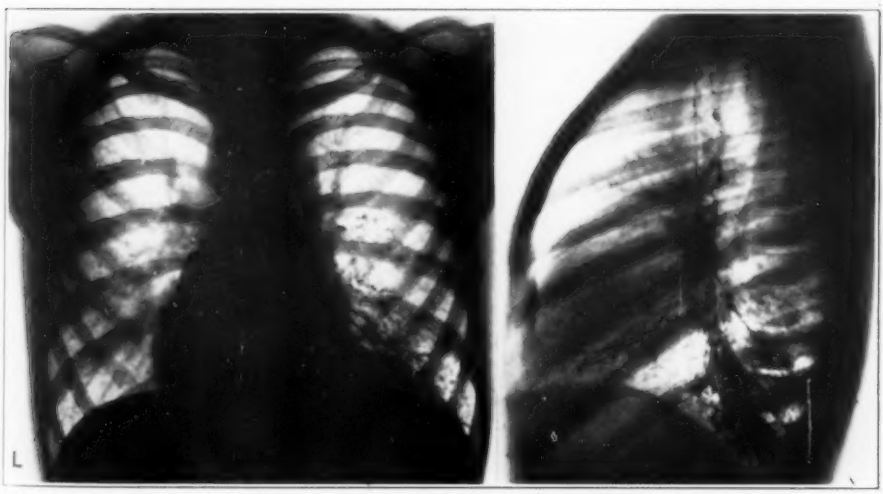


FIG. 2.—(Case I.) Roentgenogram showing anteroposterior and lateral aspects of Case I after injection of lipiodol.

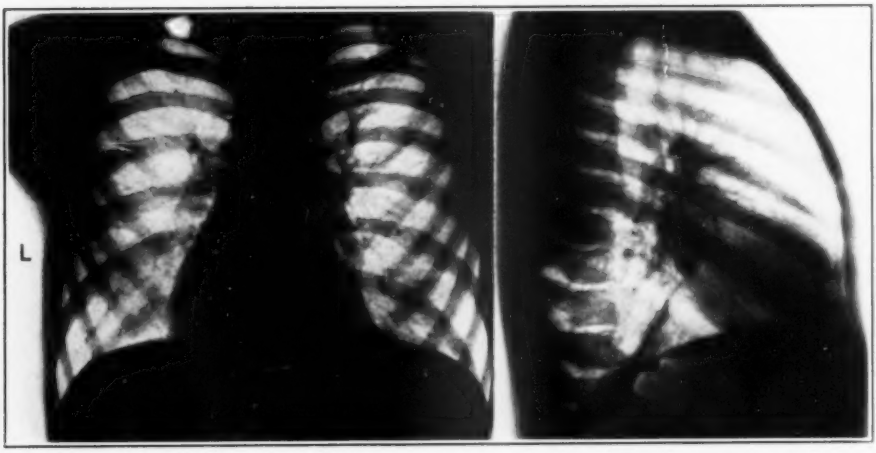


FIG. 3.—(Case I.) Roentgenograms taken after six bronchoscopic treatments of Case I. Shows considerable improvement.

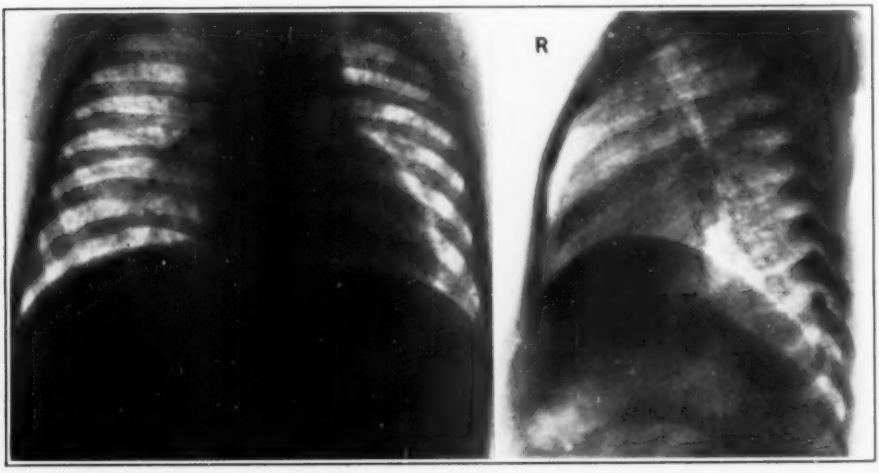


FIG. 4.—(Case II.) Roentgenograms showing very early signs of bronchiectasis and thickened interlobar pleura. Note the cordlike trunk shadows extending to the periphery of the right base.

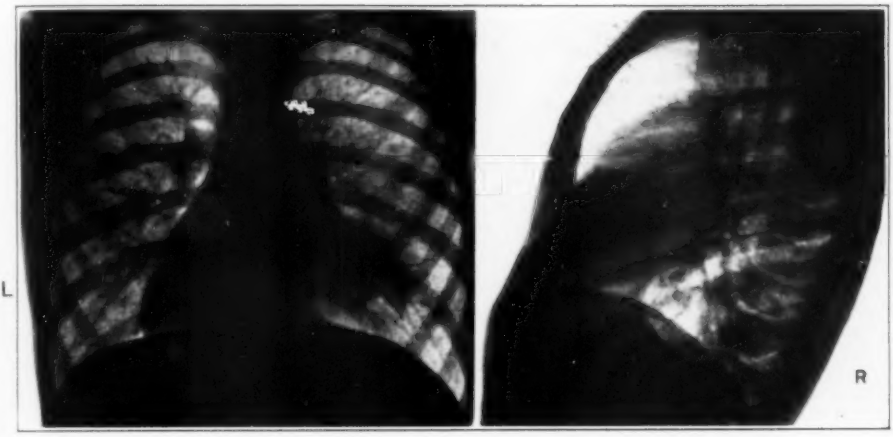


FIG. 5.—(Case III.) Roentgenograms showing early evidence of bronchiectasis at both bases. Note the huge trunk shadows extending to the periphery, especially in the lateral view.

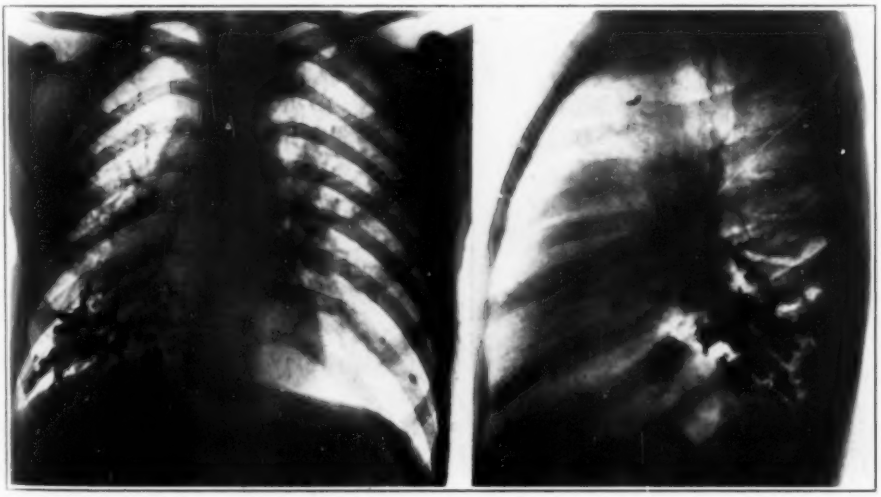


FIG. 6.—(Case IV.) Roentgenograms taken after lipiodol instillation in an advanced case. The saccular type of bronchiectasis can be seen, especially in the lateral view.

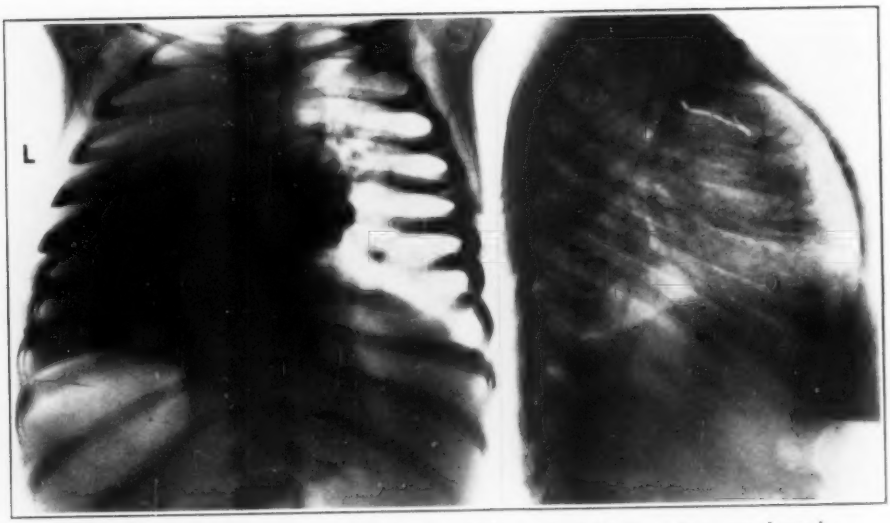


FIG. 7.—(Case V.) An advanced case which resulted fatally. Autopsy showed adhesive pleurisy, bronchiectasis and some abscess formation. Streptococcus in blood culture.

wake structural lesions in the lungs and septic pockets in the sinuses and tonsils. A vicious circle is then established and the child is never free from recurrent respiratory diseases which have either started in the lungs and augmented the upper-tract sepsis, or have been initiated in the sinuses and tonsils and have increased the intrinsic damage to the bronchial walls. Saccular bronchiectasis, abscess formation, carnification and localized empyemata are end results of the process.

Study of the causative organisms is of interest. These have been determined in all of the 27 cases which were "bronchoscoped." In no other way can an accurate investigation be made. The streptococcus was the dominant organism in 50 per cent of the cases studied, the staphylococcus in 12 per cent, Micrococcus catarrhalis in 20 per cent, the pneumococcus and influenza bacillus in 8 per cent each. Diphtheroid forms occurred in practically all cases, and from every case at least four organisms were recovered.

**Pathology.** Enough has been written concerning the final pathologic picture of chronic bronchiectasis to make it unnecessary to rehearse such a description here. It is my intention to emphasize the morbid changes which occur in early cases and not the gross lesions seen at the autopsy table. The pathology of early bronchiectasis can be seen through the bronchoscope and deduced from roentgenograms. These changes are of interest since they give clues to early diagnosis. Roentgenograms of potential cases show slight interstitial and peribronchial fibrosis at the bases only, with diaphragmatic pleurisy as an almost constant finding. Endoscopic protocols report slight annular dilatation of the bronchi, infiltration of the mucosa with loss or distortion of the glands, and residual secretion even after exhaustive coughing. This secretion is tenacious, yellow-green, mucopurulent and difficult to aspirate. Such a picture differs tremendously from the more advanced one usually presented in textbooks, lacking the saccular dilatation of the tubes, the destruction of mucosa and the quantities of foul-smelling pus.

**Clinical Considerations.** The principal symptom for which these children were brought to the hospital was cough. This cough was variable, being spasmodic and nonproductive in most of the early cases, and was incited particularly by change of position or exercise. When the sputum was produced in early cases it was yellowish, mucopurulent and tenacious. Of course, all sputum was lost in the younger children since it was swallowed. The cough in advanced cases was described as rattling and periodic, though at intervals, there would be severe paroxysms, which would culminate in the production of foul pus.

No other disease of the lungs causes hemoptysis more frequently than bronchiectasis. Blood spitting was reported as a symptom in 27 of these cases, and in 2 cough and hemoptysis preceded all

physical signs and roentgenologic findings by several months. Anorexia, asthenia and remittent fever were also repeatedly noted, while failure to gain was almost a constant symptom.

The physical signs are, broadly speaking, those of fibrosis of the lower lobes, with or without evidence of cavitation, and accompanying bronchitis. The most striking feature of these signs is their protean character. Thus, a child may show dullness, distant breath sounds and only occasional râles at one time, but at another, following a paroxysm of coughing, may present tubular or cavernous breathing with bubbling râles and wheezes. Usually there is some demonstrable impairment to the diaphragmatic function. In some the signs are those of massive pleurisy or effusion, with deformities of the chest and displacement of the heart. In early cases in which fibrosis is not extensive lagging of one diaphragm, slight impairment of the percussion note, prolongation of expiration and moist râles are the sole changes. In these a diagnosis should be made only after consideration of the history, physical signs, roentgenograms and the report from the bronchoscopist.

Definite clubbing of the fingers was noted in 29 of these 53 cases, but it is my impression that minor deformities of the nails occur more frequently, and are overlooked in all but advanced cases.

Many children, for whom no fever was reported as a symptom, showed evening rises of temperature when under hospital observation, but this disappeared following bronchoscopic and postural drainage.

The roentgenologic findings are of immense diagnostic importance. Usually an affirmative report is based upon the finding of obliteration of the lower right angle of the heart by thickened bronchial trunks which extend like cords to the periphery, and the recognition of impaired diaphragmatic action. Many advanced cases show uniformly increased density of the whole lung due to pleurisy, and can only be diagnosed accurately after the injection of lipiodol. Unilateral involvement was seen in 62 per cent of the cases, but one feels confident that bilateral disease will prove more frequent with the wider usage of lipiodol.

**Complications.** These children are especially vulnerable to recurrent bronchopneumonia, which, closely followed by pleurisy, is the commonest complication. Abscess of the lungs occurred in 7 of these cases and localized pneumothorax followed by empyema in 3. One case developed subcutaneous and mediastinal emphysema together with pneumothorax, but recovered uneventfully. One case only developed septicemia. Renal disease is apparently a noteworthy complication but no more so than in other suppurative conditions. Nineteen cases showed evidence of mild nephrosis, but 5 developed severe hemorrhagic nephritis though only 1 of the latter failed to survive. The Mantoux test was positive in only 11 of the older children, but there was no evidence at hand for connecting tuberculosis and bronchiectasis in a causal relationship.

Many of these children go about their ordinary affairs and their state of undernutrition is not recognized. Many times the initial examiner at the hospitals reported that the child under consideration was of normal development when the actual measurements proved that it was 12 to 18 per cent underweight and 1 or 2 inches underheight. Most of these cases were frail, undernourished and asthenic and a few even emaciated. Practically all showed some of the characteristic deformities of healed rickets. With only three exceptions, the whole group was below the normal standard for height and weight according to age and sex. The average subnormal variation for weight was 14 per cent, and the variation for the group ranged from 8 per cent above normal to 48 per cent below normal.

Anemia contributed to the debilitating effects of this disorder in 31 cases. In 25 the hemoglobin was below 55 per cent and transfusions were used in 18. These transfusions proved to be of great value, especially in increasing the general bodily resistance.

**Illustrative Cases.** Case I.—D. T., a male, aged seven years at admission. No familial history of tuberculosis. Breast fed for nine months; solid food was introduced after twelve months and no rachitic prophylaxis was used. Pneumonia in 1921 and 1922 followed by measles, pertussis and varicella in rapid succession. Pneumonia in 1923 and 1927. Has had repeated "colds." Tonsillectomy in 1923. History of cough, dyspnea, daily fever and failure to gain. Showed an area of dullness, distant bronchial breathing and moist râles at the right base. Moderately clubbed fingers and 8 per cent undernutrition noted. No anemia or positive tuberculin test reported. Improved after six bronchoscopic treatments coupled with postural drainage, a balanced diet and heliotherapy.

Case II.—E. L., a female, aged two years, nine months. She was examined first in the fall of 1926 and bronchiectasis has developed almost under observation. A premature baby, weighing 5½ pounds, was never breast fed, but a well-known "patent food" was used. No cod-liver oil given until the age of twelve months and then rickets was marked. This child has had six attacks of bronchopneumonia, three recurrences of otitis media and constant sepsis of the maxillary and ethmoid sinuses. Her physical signs are similar to those of asthmatic bronchitis, but sensitization tests were negative. Shows only 50 per cent hemoglobin (Sahli) and is 30 per cent underweight. Cannot walk yet. Roentgenogram shows interlobar pleurisy and the evidence of early bronchiectasis.

Case III.—I. R., a female, aged eight years. Breast fed for eighteen months; no solid food until fourteen months and never received antirachitic treatment. Severe attack of pertussis at eighteen months, said to have lasted six months; mild measles at five years; three attacks of bronchopneumonia and is almost never free from upper respiratory-tract infections. Tonsillectomy was performed at six years of age. Nonproductive cough, nasal obstruction and tardy development since infancy. Physical signs are slight impairment at the bases, lagging of the right diaphragm and occasional showers of moist râles. No anemia; is tuberculin negative, but is 10 per cent underweight. Roentgenogram shows right interlobar pleurisy with increased prominence of the trunk shadows draining the right base. Marked improvement of cough, physical signs and nutrition after three endoscopic treatments, supplemented by postural drainage, correction of her diet and adequate heliotherapy.

CASE IV.—P. C., a male, aged eight years at the first admission. The onset of paroxysmal, nonproductive cough followed influenza and bronchopneumonia. In addition he has had four other attacks of pneumonia and an attack of severe pertussis. Was diagnosed tuberculosis and sent to a sanatorium once but is tuberculin negative to 1 mg. of O. T. The cough became rattling and productive of foul pus five years ago. The signs in the chest are those of massive bilateral bronchiectasis with displacement of the heart. Roentgenograms after use of lipiodol show the saccular type of bronchiectasis on both sides. In spite of extensive involvement he has no anemia, but is 14 per cent underweight. This boy has been subjected to 250 endoscopic drainages in the past four years and shows scarcely any improvement.

CASE V.—M. V. N., a female, aged two years. Was fed on condensed milk for two years and never received cod-liver oil. She had several colds during her first year and two severe attacks of bronchopneumonia from which she has never recovered. The cough was rattling and occasionally productive. The physical signs in the chest were flatness on the left, dullness on the right, with many areas of amphoric or bronchial breathing and bubbling râles. Thorax markedly deformed. This child was emaciated, weighing only 14 pounds. The sinuses and oral cavity were badly infected and she had clubbed fingers. The blood showed marked anemia and contained nonhemolytic streptococci. This child died before she could be treated and the autopsy showed advanced bronchiectasis and abscess cavities with adhesive pleurisy.

**Treatment.** If all cases suspected of having suppurative bronchitis were bronchoscopically treated and not filled with worthless cough mixtures, bronchiectasis would actually be a rarity. Between treatments the children should have postural drainage, breathing exercises, plenty of nourishing food, cod-liver oil, fresh air and adequate heliotherapy. A comprehensive program utilizing these agents should be planned for every case and no other remedy seems to be of any use. In advanced cases vaccine therapy should certainly be tried, using an autogenous vaccine prepared from the endoscopic drainage. One cannot help pointing to the necessity of early diagnosis as an aid to efficient treatment. This is well typified by Cases I and IV, described above. The former is practically relieved after six treatments and the latter scarcely helped by 250.

Chart I shows an analysis of the 30 cases which were bronchoscoped or autopsied and in which the diagnosis cannot be questioned. The symptoms, signs, roentgenologic findings, bronchoscopic findings or autopsy findings are tabulated so as to point out the fundamental factors leading to the diagnosis. Chart II exhibits an analysis of 23 cases included in the series due to the facts that the histories, physical signs and roentgenologic findings were similar to those cases tabulated in Chart I. These cases were not studied bronchoscopically. It is hoped that in this way that the type of case to be suspected of bronchiectasis may be pointed out, and the importance of bronchoscopic study and pneumography may be emphasized.

CHART I.—ANALYSIS OF SYMPTOMS, PHYSICAL SIGNS, ROENTGENOLOGIC AND BRONCHOSCOPIC FINDINGS FOR THE 30 CHILDREN WHO WERE BRONCHOSCOPED.

| Cases | Symptoms | | | | | Phys. signs | | | | Râles | | | | Breath sounds | | | | Roentgen ray signs | | | | Bronchoscopic findings | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cough | Hemoptysis | Fever | Sweats | Wgt. loss | Expectoration | Club fingers | Under wgt. | Emphysema | Dry | Moist | Bubbling | Bronchi ves. | Bronchial. | Tubular | Amphoric | Cavernous | Density bases | Incr. bronch. trunk | Cavity | Pos. lipiodol shadow | Dilated bronchi | Suppur. bronchitis. | Cavity |
| 1 | + | ○ | + | ○ | ○ | + | + | + | ○ | ○ | + | + | + | ○ | ○ | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 2 | + | ○ | + | ○ | + | + | + | ○ | + | ○ | + | ○ | + | + | + | + | ○ | + | + | + | + | + | + | + |
| 3 | + | ○ | + | + | + | + | + | + | + | ○ | + | + | + | + | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 4 | + | ○ | ○ | ○ | + | ○ | ○ | + | + | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | ○ | + | + | ○ |
| 5 | + | + | + | + | + | + + + | + | + | + | ○ | + | + | + | ○ | + | ○ | + | ○ | + | ○ | + | + | + | ○ |
| 6 | + | ○ | + | ○ | + | + | ○ | + | + | ○ | + | ○ | + | ○ | + | ○ | ○ | + | + | ○ | ○ | + | + | ○ |
| 7 | + | ○ | + | + | + | ○ | + | + | + | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 8 | + | + | + | + | + | + | + | + | + | ○ | + | + | + | ○ | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 9 | + | ○ | + | ○ | ○ | + | + | + | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 10 | + | + | + | ○ | ○ | + | + | ○ | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 11 | + | + | + | + | ○ | + | ○ | + | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 12 | + | ○ | + | ○ | + | ○ | ○ | + | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 13 | + | ○ | ○ | ○ | + | + | ○ | + | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 14 | + | ○ | ○ | ○ | + | ○ | ○ | + | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 15 | + | + | + | ○ | + | ○ | + | + | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 16 | + | ○ | ○ | ○ | + | ○ | ○ | + | ○ | ○ | + | ○ | + | ○ | + | ○ | ○ | ○ | + | ○ | + | + | + | ○ |
| 17 | + | + | + | + | + | + | + | + | ○ | ○ | + | + | + | + | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 18 | + | ○ | + | + | + | ○ | + | + | ○ | ○ | + | + | + | ○ | + | ○ | ○ | + + | ○ | ○ | + | + | + | ○ |
| 19 | + | + | + | + | + | ○ | + | + | ○ | ○ | + | + | + | + | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 20 | + | + | + | + | + | ○ | + | + | ○ | ○ | + | + | + | + | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 21 | + | + | + | + | + | ○ | ○ | + | + | ○ | + | + | + | + | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 22 | + | + | + | + | ○ | + | + | + | ○ | ○ | + | + | + | + | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 23 | + | + | + | + | + | + | ○ | + | ○ | ○ | + | + | + | + | + | ○ | + | + | + | ○ | + | + | + | ○ |
| 24 | + | + | + | ○ | + | ○ | ○ | + | ○ | ○ | + | + | + | + | + | ○ | ○ | + | + | ○ | + | + | + | ○ |
| 25 | + | + | + | ○ | + | + | + | ○ | + | ○ | + | ○ | + | + | ○ | ○ | ○ | ○ | + | ○ | ○ | + | + | ○ |
| 26 | + | + | + | ○ | + | + | + | + | ○ | ○ | ○ | ○ | + | ○ | ○ | ○ | ○ | ○ | + | ○ | ○ | + | + | ○ |
| 27 | + | ○ | ○ | ○ | + | + | + | + | ○ | ○ | + | ○ | + | ○ | ○ | ○ | ○ | ○ | + | ○ | ○ | + | + | ○ |
| 28 | + | ○ | + | ○ | + | + | ○ | + | ○ | ○ | + | ○ | + | + | ○ | ○ | ○ | ○ | + | ○ | ○ | + | + | ○ |
| 29 | + | + | + | + | + | + | + | + | ○ | ○ | + | ○ | + | ○ | ○ | ○ | ○ | + | + | ○ | ○ | + | + | ○ |
| 30 | + | ○ | + | ○ | ○ | ○ | + | + | ○ | + | ○ | ○ | + | ○ | ○ | ○ | ○ | + | + | ○ | ○ | + | + | ○ |

Cases 18, 19, 20, 21 resulted fatally. All of them were autopsied and the lungs showed dilated, sacculated bronchi with cavity formation. Case 18 showed marked hyperplastic pleurisy with carnification of the right lung. Both lungs in this child were riddled with cavities containing purulent material. All of these cases showed areas of dullness at the bases and limitation of the movement of one or both diaphragms.

CHART II.—ANALYSIS OF FINDINGS FOR THE 23 PATIENTS NOT BRONCHOSCOPED.

| Cases | Symptoms | | | | | Phys. signs | | | Râles | | Breath sounds | | | Roentgen ray signs | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hemoptysis | Fever | Wgt. loss | Sweats | Expectoration | Club fingers | Emphysema | Under wgt. | Moist | Bubbling | Bronchial. | Tubular | Cavernous | Density bases | Incr. bronch. trunks | Cavity | |
| 1 | ○ | + | + | ○ | ○ | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 2 | + | ○ | ○ | + | + | + | + | + | + | ○ | + | + | ○ | + | + | ○ | Pleurisy |
| 3 | ○ | + | + | ○ | ○ | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 4 | + | + | + | ○ | + | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 5 | + | ○ | + | ○ | + | + | ○ | + | + | ○ | ○ | + | ○ | + | + | ○ | Interlobar pleurisy |
| 6 | ○ | + | + | + | + | ○ | + | + | + | + | + | ○ | ○ | ○ | + | ○ | Severe case |
| 7 | ○ | + | + | ○ | ○ | + | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 8 | + | + | + | + | + | ○ | ○ | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 9 | + | + | + | ○ | + | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | + | |
| 10 | + | ○ | + | ○ | + | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 11 | + | ○ | + | ○ | + | ○ | + | + | ○ | ○ | + | + | ○ | + | + | ○ | |
| 12 | ○ | + | ○ | ○ | + | ○ | ○ | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 13 | ○ | + | + | + | ○ | ○ | ○ | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 14 | + | + | + | + | + | ○ | + | + | + | + | + | ○ | ○ | ○ | + | + | Pneumothorax |
| 15 | ○ | + | + | ○ | ○ | ○ | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 16 | ○ | + | + | + | + | + | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 17 | + | + | + | + | + | ○ | ○ | + | + | ○ | ○ | + | ○ | + | + | ○ | Sinusitis mastoiditis |
| 18 | + | + | + | + | + | ○ | ○ | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 19 | ○ | + | + | ○ | + | + | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 20 | ○ | + | ○ | + | ○ | + | + | + | + | ○ | + | ○ | ○ | ○ | + | ○ | |
| 21 | + | ○ | + | + | + | ○ | ○ | + | + | ○ | + | + | ○ | + | + | ○ | Nephritis |
| 22 | + | + | + | + | + | + | + | + | + | ○ | + | ○ | + | + | + | + | |
| 23 | ○ | + | + | + | + | ○ | + | + | + | + | + | ○ | + | + | + | + | |

Cough was a symptom in all of these cases. In none of these cases were dry râles or bronchovesicular breathing noted. None of these children were bronchoscoped and none died. All of these cases showed dullness at the bases and limitation of diaphragmatic action.

**Summary.** 1. A series of 53 cases of bronchiectasis in children under thirteen years, occurring in a five-year period, is reported and analyzed. However, the opinion is advanced that this condition is far more common than is usually supposed.

2. Bronchopneumonia, pertussis and measles are the common anteceding factors in the production of bronchiectasis, since they carry infection deep into the frame work of the bronchi and lungs. Disease of the accessory sinuses is thought to be a concomitant factor in maintaining a state of sepsis.

3. An attempt has been made to demonstrate the protean nature of the disease and to correlate the physical findings with the pathologic lesions, especially in early cases.

4. Evidence has been presented showing the damaging effect of the disease on the nutritional state of the affected children.

5. A rational mode of treatment is outlined, which includes drainage of the pus-filled bronchi and care of the general health of the patient. Early diagnosis is urged to make more efficient such a therapeutic program.

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## RETROPHARYNGEAL ABSCESS IN INFANTS AND CHILDREN.

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There is a prevailing impression that retropharyngeal abscess is uncommon in infants and children, and that when it does occur, the diagnosis is easily and readily made. Our experience, however, leads us to believe that the condition more frequently escapes recognition than any other acute disease in childhood. In fact, every child in our series was brought to our attention with the condition undiagnosed and had been treated for from one to three weeks with no suspicion of the correct diagnosis. This may perhaps be partly explained by the fact that when the general practitioner diagnoses the disease he refers the patient at once to a throat specialist. It is

the purpose of this paper to emphasize the relative frequency of retropharyngeal abscess in infants and children and to advance the methods employed by us in making a diagnosis of retropharyngeal abscess.

The history of retropharyngeal abscess dates back to Hippocrates who mentions it in his book *On the Prognostics*.[1] "Those quincies . . . such as . . . are attended with pain, are swelled up, and have redness in throat are indeed very fatal. . . . It is much less hazardous when the swelling and redness are determined outwardly, but if determined in the lungs they superinduce delirium, and frequently some of these cases terminate in empyema." Galen,[2] in the second century, relates a case which occurred in his experience and which terminated in spontaneous rupture. From his manner of alluding to the case it appears that he had seen several examples of this kind, most of which ended fatally. Centuries later, Morgagni[2] described a case which caused death by rupture into the trachea. In 1785, Bleuland[2] mentioned that his master, Van Doeveren, had seen a case which terminated fatally.

C. Fleming[3] was the first to make a study of retropharyngeal abscess. He published his results in 1840, two years prior to Verneuil[4] who also gave an accurate description of the disease. Roustan[5] (1869), Gautier[6] (1869), and von Schmitz[7] (1873) added their studies. Gautier called the affection "angine phlegmoneuse," Roustan, "adenite suppurée retropharyngienne;" the latter, therefore, may be classed among the first to view the disease as a suppurative lymphadenitis. These early observers, while conceding that a retropharyngeal lymphadenitis might precede a retropharyngeal abscess, thought that this sequence was the exception. It was the elder Bokai[8] who first viewed retropharyngeal abscess as invariably coming from a lymphadenitis—a conception which experience has shown to be correct.

**Anatomy.** The retropharyngeal lymph nodes were first described by Mascagni. In his work, "Vasorum lymphaticorum corporis human. hist. et iconographi" (1785, page 63), he described them as "glandulæ . . . quae ad latus internum carotidis internæ resident propre ipsium ingressum in canalum coroticum." Most anatomists (Merkel, Luschka, Sappey) called them retropharyngeal glands, although Henle described them as the deep facial glands.

There is considerable disagreement as to the number of glands included under the term retropharyngeal lymph nodes. Poirier and Cuneo[9] state that usually they are two in number. Most's[4] very accurate researches on the topographical anatomy of these glands led to the following conclusions: In the newborn, there is in the majority of cases only one gland; in a few cases, two; very seldom more. Topographically they belong to the deep cervical chain of glands.

These nodes, embedded in loose areolar tissue, are located behind the pharynx at the level of the atlas and at the junction of the

posterior and lateral walls of the pharynx. Anterior to these glands is the posterior wall of the pharynx. Posteriorly they are separated from the lateral masses of the atlas by the rectus capitus anticus major muscle. Externally they are in relation with the constrictors of the pharynx and through these with the internal carotid artery. Internally, they are nearly 2 cm. distant from the midline of the pharynx. The retropharyngeal glands receive afferents from almost all the collectors of the mucosa of the nasal fossæ and their accessory sinuses, the lymphatics of the nasopharynx, those of the Eustachian tubes and perhaps some of the lymphatics of the cavity of the tympanum. The efferent vessels of the retropharyngeal glands empty into the internal glands of the deep cervical chain. Since the retropharyngeal glands do not drain the palatine tonsils, infections of the latter can reach these glands only indirectly, namely, through involvement of the neighboring pharynx. After the first year of life, they undergo retrogressive changes, but persist, as a rule, until later in childhood, as is evidenced by the number of cases of retropharyngeal abscesses that occur in children over one year of age.

**Pathogenesis.** Anatomical studies explain the progress of a case of retropharyngeal abscess. The first stage of the disease is infection of one of the points drained by the retropharyngeal glands. This usually is an adenoiditis, though rarely rhinitis, sinusitis, or otitis may also usher in the disease. When the infection spreads to the retropharyngeal glands there results an adenitis with an accompanying periadenitis which frequently is followed in twenty-four to forty-eight hours by suppuration. At times, however, the disease does not progress beyond the stage of lymphadenitis, pus formation does not occur and resolution takes place.

Retropharyngeal abscess may conveniently be classified as primary and secondary. The most frequent variety is the primary or idiopathic (Bokay[10]). It is preceded, as a rule, by a nasopharyngitis, although occasionally the accessory nasal sinuses and the middle ear are the portals of entry. The secondary retropharyngeal abscesses follow infection of the upper cervical vertebræ (Pott's disease), or migration of pus from a superficial cervical adenitis or, what is still rarer, a metastasis from a distant abscess. A rare cause of secondary retropharyngeal abscess is a cavernous sinus thrombosis. According to Eagleton,[11] the postpharyngeal suppuration originates from retrograde thrombophlebitis of the veins communicating with the cavernous sinus and the pharynx. In fact, Eagleton states that when a retropharyngeal abscess is encountered during the course of an attack of otitis media in a patient over eighteen months of age cavernous sinus should be suspected. At times retropharyngeal abscess follows trauma; the traumatic type is encountered only exceptionally and is usually due to a foreign body, as a rule a fish bone, lodging in the posterior pharynx, though occasionally tonsillectomy is the etiologic factor. Numerous examples of each variety have been reported in the literature.

**Sex.** This is not an important factor, the cases being equally divided.

**Age.** Retropharyngeal abscess is a disease of childhood. The reason for this is that the retropharyngeal glands undergo retrogressive changes after the first year of life. Von Schmitz[7] found no, or at most one, gland in this region after the third year. The researches of Most[4] agree with this view. The smaller glands behind the pharynx are never found in adults and the main lateral retropharyngeal glands atrophy until they are no larger than a bean; and are, therefore, easily overlooked.

Retropharyngeal abscess is most frequent between the ages of two months and four years. In Bokay's[10] series 94 per cent of the cases occurred during the first three years of life. Vas,[12] continuing this series, found 59 per cent of the 1054 cases occurring in the first year of life; 35 per cent between the first and third and less than 1 per cent after the seventh year. Guthrie[13] in a series of cases reported the following statistics:

| | Cases. | Per cent. |
|---|---|---|
| 0 to 1 year | 7 | 35 |
| 1 to 2 years | 4 | 20 |
| 2 to 3 years | 3 | 15 |
| 3 to 4 years | 2 | 10 |
| 4 to 5 years | 1 | 5 |
| 5 to 6 years | 1 | 5 |
| 6 to 7 years | 2 | 10 |
| Total | 20 | |

Babbitt[14] found that 60 per cent of his 50 cases of retropharyngeal abscess occurred in the first year of infancy:

| | Cases. | Per cent. |
|---|---|---|
| 0 months to 6 months | 8 | 16 |
| 6 months to 1 year | 25 | 50 |
| Second year | 13 | 26 |
| 2 to 2½ years | 1 | 2 |
| 2½ to 4 years | 1 | 2 |
| 4 to 6 years | 1 | 2 |
| 6 to 10 years | 1 | 2 |
| Total | 50 | |

Similar findings are recorded by Frank.[15] Seventy of his 74 cases occurred in children under ten years of age and 90 per cent in children under three years of age. In our series of 55 cases, 22, or 40 per cent, occurred in infants under one year of age; 25 cases were found between one and two years of age; the remaining 8 were distributed as follows:

| | Cases. | Per cent. |
|---|---|---|
| 0 to 1 year | 22 | 40.00 |
| 1 to 2 years | 25 | 45.00 |
| 2 to 3 years | 2 | 3.63 |
| 3 to 4 years | 1 | 1.81 |
| 4 to 5 years | 2 | 3.63 |
| 5 to 6 years | 2 | 3.63 |
| 6 to 7 years | 1 | 1.81 |
| Total | 55 | |

Eighty-five per cent of our cases were, therefore, under two years of age. This agrees with former statistics. The oldest child that we have seen with this affection was seven years of age and the youngest five weeks of age. The great majority of our cases occurred in children under two years of age.

**Season.** The disease occurs most frequently in the spring and winter months. The reason for this is evident: upper respiratory infections are most common in these months.

**Associated Diseases.** Retropharyngeal abscesses occur occasionally during or after the acute infectious diseases. Of Bokay's[10] 926 cases, 14 occurred during an attack of scarlet fever; one during measles and two during diphtheria of the pharynx. The abscesses complicating the exanthemata are, as a rule, malignant and have a tendency to burrow downward into the mediastinum. Syphilis is mentioned by some authors as an etiologic factor. Bokay[10] observed 8 cases due to syphilis. These are, however, the exception. The influence of constitutional diseases, such as rickets or the scrofulous diathesis, on the development of retropharyngeal abscess is indefinite and very doubtful. The only associated or complicating diseases in our series were the initial nasopharyngitis and the subsequent otitis media.

**Bacteriology.** In 1894 Koplik[16] studied 8 cases of retropharyngeal abscess bacteriologically and succeeded in isolating a streptococcus in all. In one case he found, in addition the Bacillus lactis aërogenes, which was probably a contamination from the mouth. These findings have since been repeatedly corroborated.

**Symptoms.** The onset is usually insidious. In the majority of cases, there is a preceding nasopharyngitis, which produces a wide range of symptoms; after a lapse of from two to four days the first symptoms of retropharyngeal abscess appear. The time elapsing between the appearance of the first symptom and the time of diagnosis varies. It may be only two days and it may be three weeks. The average is about ten days.

Most textbooks mention difficulty in swallowing as the first symptom. This has not been our experience. The earliest symptoms in our cases were either restlessness, fever or an enlarged cervical gland. We wish to emphasize particularly the presence of a unilateral cervical adenitis. The enlarged gland is usually situated at the angle of the jaw at the posterior border of the sternocleidomastoid muscle. In 2 cases, the enlarged gland was anterior to the angle of the jaw and almost in the midline. The presence of an enlarged gland in these regions should always lead one to suspect a retropharyngeal abscess and to exclude it, if possible, by the only absolute method of diagnosis, namely, palpation of the throat.

Difficulty in swallowing is a very important symptom, although it must be emphasized that it is not a very early one and occurs relatively late in the disease. Young infants show it by refusing all

food. Thus, an infant will take the breast very eagerly, suck it a few times, then let go, throw the head backward, eject the milk from the mouth and cry bitterly. One must be on guard not to attribute such a refusal of food to colic. We have seen a four-month-old infant, suffering from retropharyngeal abscess, treated for one week for colic, because it appeared to be in pain when taking the breast.

At first the pain on swallowing is caused by inflammation. Only later, when the abscess obstructs the pharyngeal cavity, does the mechanical factor come into play. Mechanical obstruction is most marked in the rare case where the abscess is in the midline; it is also prominent in lateral abscesses that are so large that they approach the midline. In our series of cases, not one abscess was found directly in the midline. All were lateral. This fact may account for the absence of dysphagia as an early and predominating symptom. Infants may become dehydrated very rapidly unless proper measures are taken to supply them with fluid. Dystrophy may result if the abscess is of long-standing. Since the pharynx is smaller in infants than in older children, the younger the child the more marked will dysphagia be. Occasionally, however, nourishment is not refused even though the condition is advanced.

The voice, too, changes. It loses its natural tone and becomes nasal in quality. When the child cries or talks, the voice assumes a peculiar muffled quality as if there were a hot potato in the mouth. This becomes more and more definite as the affection progresses. The voice change differs from that found in palatine paralysis following diphtheria, in that in the latter disease the voice is flatter, weaker, and lacks the deep gurgling qualities found in cases of retropharyngeal abscess.

Respiratory difficulty is present in almost every case and occasionally causes diagnostic errors. Careful observation of the type of respiratory embarrassment will often give a clue to the level of the abscess. If the abscess is located in the upper part of the pharynx, nasal breathing is impossible and the child becomes a mouth breather. An abscess at the level of the epiglottis will cause respiratory difficulty simulating that found in laryngeal stenosis, due to diphtheritic laryngitis or to foreign body in the larynx. Only when the possibility of retropharyngeal abscess is kept in mind and the throat is palpated is the true condition revealed. Due to the difficulty in swallowing, mucus collects in the throat and causes the rattling and stertorous breathing so frequently heard. In fact, the snoring, gurgling respiration during sleep is one of the most constant symptoms of retropharyngeal abscess. All these symptoms are aggravated when the patient is in a horizontal position. Again, the younger the patient and the more rapid the course of events, the more pronounced are these findings.

Torticollis is a symptom found in nearly every case and, when

present, should always lead one to rule out retropharyngeal abscess before a search is made for other causes. In one of our cases, torticollis was the outstanding symptom and was present for six weeks. It was so marked that roentgenologic examinations had been made to rule out vertebral pathology. This symptom was present in 80 per cent of our cases. Early in the disease there is a definite stiffness of the neck. A little later the head becomes inclined toward the affected side and in the last stages the neck is held immovable and backward to facilitate breathing.

The temperature is very rarely high. In most cases it ranges between 100° and 102.5° F. In only one of our cases was the temperature elevated above 103° F.

**Physical Examination.** When the child is brought for examination, one notes at once that he looks ill. As a rule, the head is held to one side, the mouth is open and dribbling is present. Rarely, facial paralysis is noted. When retropharyngeal abscess is suspected a careful examination of the glands of the neck should be made. Usually only one gland is enlarged. It may be situated anterior or posterior to the sternocleidomastoid muscle. At times, however, a whole chain of glands may become enlarged and late in the disease they may become matted together. When this occurs, the mass is very large and extends well down into the neck. When only one gland is involved, the enlargement may be so small as to escape superficial examination. If, however, the thumb and forefinger are hooked about the anterior and posterior borders of the sternocleidomastoid muscle the slightest increase in size can usually be detected. The glands, whether small or large, are usually hard; rarely, fluctuation occurs late in the disease when the abscess has ruptured outwardly.

It is necessary to have a clear conception of a normal throat in infants and children in order to determine, from the brief glance that is afforded the examiner, whether pathologic changes exist or not. Inspection of the throat in infants is rarely conclusive. In older children, difficulty is encountered in the examination because of trismus. The pushing forward of one pillar is one of the most constant signs found on inspection and one that may easily be overlooked. At times also a slight edema of the soft palate may be noted on the involved side. The edema, however, never reaches the extent found in peritonsillar abscess. Frequently the mucous membrane of the throat appears dry and congested. The mucosa covering the swelling is at first red and later, as suppuration occurs, the redness fades and the pharyngeal wall becomes pale and finally yellowish. When the abscess is large enough the soft palate and uvula are displaced laterally and forward. In cases where tonsillectomy has previously been performed the mass may be seen behind the anterior pillar, filling in the empty tonsillar space.

Frequently inspection reveals nothing and resort to digital

examination must be made to establish the diagnosis. In young infants, this offers no difficulty. In older children, care is necessary to prevent injury to the examiner's finger through biting. A mouth gag should not be used since sudden death, due to asphyxia, has been reported following its use. Our procedure is to use a metal finger which is placed on the index finger of the left hand and inserted between the upper and lower jaw at the first and second molars. This suffices to pry the mouth open wide enough to admit the index finger of the right hand which is swept about the pharynx. In the stage of lymphadenitis one finds to one side of the midline a tender, firm, resistant mass, smooth in outline, varying in size from a bean to a hazelnut. If suppuration is present, the mass feels elastic and boggy. When an abscess is present, the vertical and lateral extent is noted. The whole procedure should take only a few seconds. When done in this manner we have never seen any ill effects from digital examination. Occasionally, the prominence of the body of the seventh cervical vertebra is marked and unless care is taken it may be mistaken for lymphadenitis. In fact, this mistake was made in one of our cases. The deeper location and the bony hardness of the vertebra should prevent error. We wish to emphasize that all manipulation should be done gently to prevent rupture of the abscess and resulting suffocation of the patient. Thus, Koplik[17] reports a case in which death followed within a few hours after pus was aspirated from an abscess which burst as a result of rough digital examination. Rarely, collapse follows digital examination.

The following table is an analysis of the symptoms recorded and of the signs observed in our cases. As may be seen, fever, restlessness and enlarged cervical glands occurred in every case. The fever in nearly every instance was of moderate degree. Voice changes were found in only a small number of cases; this may be attributed to the fact that the abscess in most of our cases had not reached large proportions.

| Symptoms. | Cases. |
|---|---|
| Fever | 55* |
| Restlessness | 55 |
| Cervical adenopathy | 55 |
| Respiratory difficulty | 41 |
| Difficulty in swallowing | 35 |
| Torticollis | 44 |
| Mass in back of throat: | |
| Lateral | 55 |
| Medial | 0 |
| Retropharyngeal abscess | 53 |
| Retropharyngeal lymphadenitis | 2 |
| Complicating otitis media | 8 |

* Temperature 102° F. or less in 49; 102° F. or more in 6.

**Complications and Sequelæ.** If the abscess is left to itself, it may pursue any one of four courses: (1) It may burst spontaneously and

drain into the larynx. This is not uncommon, Bokay, Sr., having seen it nineteen times in 144 cases. The danger of this is the possibility of the pus gaining entrance into the tracheobronchial tree and causing sudden death, due to asphyxia; or multiple abscesses of the lung with fatal termination may result. Indeed, Babbitt[14] believes that many cases of unexplained sudden asphyxia may be due to inspiration of pus from a ruptured retropharyngeal abscess. Myerson[18] reported a case of spontaneous rupture of a retropharyngeal abscess which flooded the lungs. The child was given artificial respiration and a tracheotomy was done. A catheter attached to a suction apparatus was passed through the tracheotomy tube and the pus aspirated. The child made an uneventful recovery. We have observed several cases of spontaneous rupture with recovery, but we have never seen asphyxia resulting from rupture. It may be assumed that rupture has occurred in a case of retropharyngeal abscess when there is a sudden disappearance of the enlarged external glands and an immediate amelioration of symptoms. (2) The pus may burrow inwardly instead of being evacuated through the pharynx, dissecting the tissues laterally to the side of the neck behind the large vessels and the sternocleidomastoid muscle, and appear at the posterior triangle of the neck. If the abscess ruptures through the surrounding prevertebral fascia it may present itself anteriorly to the sternocleidomastoid muscle in the anterior triangle of the neck. (3) Instead of burrowing laterally the pus may extend downward along the prevertebral fascia into the lower part of the neck. This complication has been reported by Mercier.[19] In his patient, the pus made its way through the tissues of the neck and opened at the level of the clavicle. (4) Rarely, the pus is guided behind the esophagus into the posterior mediastinum. A very rare route for the escape of pus is reported by Szmurl.[20] In his patient, the abscess burrowed through the internal auditory canal into the cranial cavity.

A relatively infrequent and serious complication is erosion of one of the main bloodvessels in the vicinity of the abscess. The vessels most likely to be involved are the internal carotid artery and, to a lesser extent, the internal jugular vein and the vertebral artery (the latter only in cases secondary to tuberculous cervical spondylitis). There are several reports in the literature describing cases of fatal hemorrhage from the carotid artery,[21] occurring immediately after incision of the abscess. In isolated cases[22] it has been possible to avert a fatal outcome by an immediate ligation of either the common or internal carotid artery. Not always, however, is the source of bleeding evident. Thus, Wishart[23] reports the case of a child eighteen months of age who had two severe hemorrhages from the mouth which were assumed to be of gastric origin. At the postmortem examination a large retropharyngeal abscess with erosion of the internal carotid artery was discovered. In one of our fatal cases,

the cause of death was hemorrhage due probably to an erosion of the internal carotid artery. This occurred in an infant six months old, who, a week after an attack of nasopharyngitis, developed a retrophayngeal abscess. This case was referred to a nose and throat surgeon who opened the abscess with a sharpened finger nail. As the finger was removed there was a violent gush of blood from the mouth and the child died within a few minutes. We have never encountered a case in which the internal jugular vein was involved. Mosher,[24] however, described a case of retropharyngeal abscess which ran a septic temperature after incision of the abscess. At the time of the second operation the internal jugular vein was found to be thrombosed and about 2 inches of the vein had sloughed away. Equally rare is erosion of the vertebral artery. It occurs only in cases of abscess secondary to vertebral inflammation and may cause fatal hemorrhage.

**Prognosis.** Retropharyngeal abscess is a benign disease if recognized early and treated properly, but dangerous and even fatal if unrecognized.

The time of diagnosis affects the prognosis: the earlier the diagnosis is established and proper treatment instituted, the better the prognosis. Operation should be deferred until definite fluctuation can be detected. We have had one fatality due to a failure to recognize the fact that a retropharyngeal lymphadenitis should never be incised before the stage of suppuration. This occurred in an infant eight months of age who, ten days after an attack of nasopharyngitis, refused food, cried when forced to eat, and snored while sleeping. Examination showed the cervical gland on the left side to be enlarged and tender. A firm, tender, mass was palpated in the left posterior wall of the pharynx. The mass was incised; after the operative interference the general condition became rapidly worse, swallowing became impossible, the temperature rose to 104° F., and attacks of cyanosis occurred. Four days after the incision the child died, presenting the picture of a profound sepsis.

The influence of constitutional disturbances or of accompanying infections on the prognosis is evident and needs no discussion.

As a rule, the mortality rate of retropharyngeal abscess is low. In Bokay's[10] series there were 14 deaths in 317 cases. In our series of cases, the mortality rate was somewhat higher (7.3 per cent), 4 deaths occurring in a series of 55 cases.

**Treatment.** Treatment will depend entirely upon the stage in which the disease is first observed. If the patient is seen during the stage of lymphadenitis, mild alkaline sprays or gargles are indicated. Local applications of equal parts of glycerin and alcohol to the neck may be of use. Operative procedure is absolutely contraindicated in this stage. As soon as fluctuation is present the mass should be incised. In our cases the internal route was used almost without exception. External incision anterior to the sternocleidomastoid

muscle has also been advocated. According to Bokay, Jr.,[10] this method of approach was first practised by St. Germain in 1872. In the hands of some men, it has given good results. Thus, Schmidt[25] treated 15 cases of retropharyngeal abscess (13 primary and 2 tuberculous) by the external route with no unpleasant incidents either during the operation or subsequently. We believe this method should be used only in cases secondary to cervical Pott's disease or in cases where the abscess is situated low down in the pharynx. In the latter case there is too much danger of some of the pus spilling into the larynx when the abscess is opened through the mouth. That the internal route is not without danger may be seen from reports of cases of sudden death following operative interference.

On the whole, however, immediate improvement follows incision. As a general rule, within twenty-four hours the glandular enlargement disappears to a great extent. The child shows a rapid improvement in its general condition and takes nourishment readily and eagerly. The improvement usually progresses until complete recovery takes place. A recurrence of symptoms after incision usually points to the closure of the operative opening and is an indication for reëstablishment of drainage.

**Summary and Conclusions.** 1. A series of 55 cases of retropharyngeal abscess is reported and analyzed and the literature reviewed.

2. The condition is not uncommon in early infancy and childhood. It is more common in the first year of life than later. It is equally divided between the sexes and occurs most frequently in winter and spring, when respiratory infection is commonest.

3. Retropharyngeal abscess should be suspected in every case presenting an enlarged cervical gland and the diagnosis should be determined by a digital examination of the pharynx.

4. Retropharyngeal abscess is not an innocuous disease as demonstrated by the fact that the mortality rate was 7.3 per cent in our series.

5. The danger of operating in the stage of non-suppurative lymphadenitis as well as the dangers of not operating when fluctuation is present are pointed out.

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## THE PANCREATIC TRIAD.*

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Our previous experiments, performed on dogs with the help of E. W. and A. W. Boldyreff,[1-4] have shown that either a complete pancreatectomy or a severe loss of pancreatic juice through a fistula of the main pancreatic duct involve the following three pathologic conditions to which we have affixed the name "Pancreatic Triad:"

1. A rise in the percentage of the blood sugar (that is, a decrease in the content of glycolytic ferment in the blood).[2]

2. A decrease of the blood coagulability—apparently due to decrease in the content of fibrin ferment in the blood;[3] and

3. The appearance of leukocytosis.[4]

Our numerous experiments on dogs have convinced us that complete loss of pancreatic juice (complete diversion to the outside) produces in general the same phenomena in the organism as does

* Reported to the American Physiological Society, Ann Arbor, Michigan, April 13, 1928.

complete pancreatectomy. In order to understand why this is true, one should recall that in normal conditions the pancreatic juice secreted into the intestine is immediately absorbed therefrom into the blood (as shown by our experiments—both those previously published and those described in this paper) and then enters the organism, supplying its tissues with all its ferments. But when the juice is discharged outside the organism, there is a lack of all pancreatic ferments. Thus, complete loss of pancreatic juice could be called physiologic pancreatectomy. One must believe that in anatomic (or surgical) pancreatectomy the chief cause of the diseased conditions following the operation is the deprivation of the body of the pancreatic juice.

In 1913, Dr. V. N. Vorobiev and I[5] produced fistulæ of both pancreatic ducts (dog), so that all the pancreatic juice was flowing outside the body. Within twenty-four hours after the operation azoturia and glycosuria appeared, and the wound remained open for some time. (After the fistulæ were finally closed the dog quickly recovered.) All this, together with other known symptoms, is also observed in cases of complete pancreatectomy. We are still continuing these experiments and intend to treat such animals by the introduction of pancreatic juice through an intestinal fistula. I first recommended the use of pancreatic juice as a remedy in 1914.[5] In my lectures at the Universities of Kyoto, Tokyo, Osaka and Fukuoka, I repeated this recommendation many times (1920–1921); Hedon's experiments confirm the correctness of such a view.[6]

The duration of the three phenomena which we have termed the "Pancreatic Triad" depends on the conditions of the experiment and varies in different cases from several hours to several days or more, as may be seen in Tables I and IV.

TABLE I.—RESULTS OF TOTAL PANCREATECTOMY ON A DOG.

| No. of test. | Time in minutes. | Leukocytes in thousands per c.mm. | Blood-congulation time in seconds. | Blood sugar in per cent. |
|---|---|---|---|---|
| | Before the Operation (Normal). | | | |
| I | .. | 10.8 | 45 | about 0.10 |
| | After the Operation. | | | |
| I | 15 | 7.0 | 30 | |
| II | 150 | 12.0 | 75 | |
| III | 270 | 20.1 | 120 | 0.17 |
| IV | 540 | 20.3 | 180 | 0.21 |
| | 500 cc. blood taken out. | | | |
| V | 600 | .. | 240 (!) | |

Experiment by E. Boldyreff and A. Boldyreff, February 26, 1925. Dog kept without food for twenty-four hours before experiment. Subcutaneous injection of 0.025 gm. morphin. Chloroform-ether-alcohol anesthesia.[1]

Leukocytosis is notoriously easy to produce in the dog, and similar figures are the rule after narcosis and abdominal operation (see Krumbhaar[7]). The decrease in coagulability is striking.

Our new experiments (Table II) performed on many dogs and new observations made on several men have confirmed former ones and have shown that this pathologic triad may also be a consequence

TABLE II.—TOTAL PANCREATECTOMY POSTOPERATIVE RESULTS OF NEW DOG EXPERIMENTS (E. BOLDYREFF).

Dog N1a. Young female, 8.900 gr.

| Time of observation | Normal (before operation) | 5 hours postoperative | 8 hours postoperative |
|---|---|---|---|
| Blood-coagulation time in seconds | 55 | 70 | 90 |
| Leukocytes | 6,500 | 19,700 | |
| Blood sugar | 0.095 | 0.112 | 0.132 |

Dog N2a. Female six months, 9.570 gr.

| Time of observation | Normal before operation | 12 hours post-operative | 24 hours post-operative | 31 hours* post-operative | 44 hours post-operative | 56 hours post-operative | 72 hours post-operative |
|---|---|---|---|---|---|---|---|
| Blood-coagulation time in seconds | 45 | 65 | 180 | 230 | 230 | 150 | 45 |
| Leukocytes | 6,800 | 23,100 | 17,000 | 18,100 | .. | 7,900 | 6,800 |
| Blood sugar | 0.125 | 0.34 | 0.44 | 0.30 | .. | 0.21 | |

Dog N3a. Male nine months, 13.620 gr.

| Time of observation | Normal before operation | 23 hours post-operative | 28 hours* post-operative | 47 hours post-operative | 56 hours post-operative |
|---|---|---|---|---|---|
| Blood-coagulation time in seconds | 140 | 240 | 210 | 60 | 60 |
| Leukocytes | 8,800 | 26,000 | 20,000 | 15,100 | 21,000 |
| Blood sugar | . | 0.39 | | | |

* The time of first feeding after the operation.

of other defects in the function of the pancreas; thus, after a partial pancreatectomy, when about a quarter or a third of the gland is removed, no matter whether from the head or the tail, we observed a temporary appearance of all three symptoms (Table III).

In the other 8 cases of total pancreatectomy we obtained approximately the same results. In all our experiments described in this paper, the dogs were provided with an ample supply of drinking water.

In every case the tail of the pancreas (about 6 gm.) was removed. Removal of the head of the pancreas had the same effect, as was shown by our experiments.

TABLE III.—PARTIAL PANCREATECTOMY.

Dog No. 12.

| Time of observation | Normal before operative | 24 hours* post-operative | 48 hours post-operative | 56 hours post-operative | 72 hours post-operative | 144 hours post-operative | 168 hours post-operative |
|---|---|---|---|---|---|---|---|
| Blood-coagulation time in seconds | 30–45 | 30 | 360 | 405 | 150 | 45 | 45–50 |
| Leukocytes . . | 7700 | 18,200 | 9300 | 8600 | . . | 6800 | 8500 |

Dog No. 21.

| Time of observation | Normal before operation | 24 hours* post-operative | 48 hours post-operative | 72 hours post-operative | 96 hours post-operative | 120 hours post-operative | 144 hours post-operative |
|---|---|---|---|---|---|---|---|
| Blood-coagulation time in seconds | 30 | 60 | 75 | 180 | 35 | 30 | 25 |
| Leukocytes . . | 4300 | 15,900 | 8700 | 9800 | 6700 | 5800 | 4700 |

Dog. No. 29.

| Time of observation | Normal before operation | 24 hours* post-operative | 48 hours post-operative | 72 hours post-operative | 96 hours post-operative | 120 hours post-operative | 144 hours post-operative |
|---|---|---|---|---|---|---|---|
| Blood-coagulation time in seconds | 45 | 45 | 90 | 75 | 75 | 50 | 30 |
| Leukocytes . . | 5400 | 8800 | 8900 | 6200 | 7300 | 6600 | 6400 |

Dog No. 30a.

| Time of observation | Normal before operation | 24 hours* post-operative | 48 hours post-operative | 96 hours post-operative | 120 hours post-operative | 144 hours post-operative |
|---|---|---|---|---|---|---|
| Blood-coagulation time in seconds . . . . . | 40 | 30 | 45 | 60 | 30 | 30 |
| Leukocytes . . . . . | 6400 | 15,800 | 15,200 | 20,900 | 12,900 | |

* The time of first feeding after the operation.

In several cases the blood sugar was determined and an increase in its amount was found.

We next observed the triad in dogs as a consequence of both the ligation of pancreatic ducts or of the main duct only; even a temporary closure of both pancreatic ducts with clamps may produce the same phenomena (Tables V and VI). Last, and very recently, we have met with the above-mentioned triad (rise of blood sugar, leukocytosis, delayed blood coagulability) in cases of diabetes both

in dogs and in men (Tables VII and VIII). The figures obtained from experiments on dogs follow:

TABLE IV.—PANCREATIC TRIAD IN CASES OF PANCREATIC FISTULA.

Dog N5a.

| Time of observation | Normal before operation | 72 hours post-operative | 144 hours post-operative | 168 hours post-operative | 192 hours post-operative |
|---|---|---|---|---|---|
| Leukocytes | 6900 | 5100 | 14,400 | 17,000 | 18,200 |
| Blood sugar | 0.1 | 0.14 | 0.16 | .. | 0.24 |

On nine other dogs with pancreatic fistula, we obtained similar results.

In several dogs with pancreatic fistulæ, we observed that for several days after the operation the pancreatic juice did not secrete. During this time, the triad was absent on these dogs but it appeared as soon as the pancreatic juice began to flow abundantly from the fistula. As would be anticipated, we failed to observe the triad of symptoms following other types of operation on the digestive tract, as, for instance, gastric fistula, biliary fistula, etc. (Table V).

TABLE V.—PANCREATIC TRIAD UNDER VARIOUS CONDITIONS.

| Dog. | Date. | Normal. | After a ligation of both pancreatic ducts. | | |
|---|---|---|---|---|---|
| | | 3-28-27 | 4-1-27 | 4-5-27 | 5-3-27 |
| 6a | Leukocytes | 7500 | 16,800 | .. | 8500 |
| | Blood coagulability in seconds | 30 | 170 | .. | 120 |
| | Blood sugar | 0.095 | 0.118 | 0.120 | 0.095 |

| | Date. | Normal. | After ligation of main pancreatic duct. | | | | |
|---|---|---|---|---|---|---|---|
| | | 1-24-24 | 1-25-24 | 1-27-24 | 1-28-24 | 1-29-24 | 1-30-24 |
| 7a | Leukocytes | 6000 | 17,700<br>16,400 | 13,400 | 16,900 | 9500 | 8300 |

| | Date. | Normal. | After operation for gall-bladder fistula. | | | |
|---|---|---|---|---|---|---|
| | | 3-28-27 | 3-31-27 | 4-1-27 | 4-5-27 | 5-12-27 |
| 7b | Leukocytes | 6600 | 6900 | 12,300 | 6600 | |
| | Blood coagulability in seconds | 25 | 25 | 25 | 25 | |
| | Blood sugar | 0.100 | .. | 0.091 | 0.090 | 0.100 |

Three cases are presented in Table V. In the Dogs 6a and 7a the pancreatic ducts were ligated and we observed the usual symptoms. Dog 7b, with a fistula of the gall bladder, was operated upon the same day as Dog 6a, with ligation of both pancreatic ducts. Although both operations were technically quite similar and were done nearly on the same anatomic region, Dog 7b (biliary fistula) showed no phenomena of the triad except for a brief leukocytosis, but Dog 6a showed the presence of all members of the triad.

TABLE VI.—PANCREATIC TRIAD (AFTER CLOSING BOTH PANCREATIC DUCTS).

Young Dog (8a), Ether Anesthesia.

| | | Normal | Ducts clamped | Ducts open |
|---|---|---|---|---|
| I | Leukocytes | 7100 | 12,200 | 9600 |
| II | Blood-coagulation time in seconds | 30 | 120 | 45 |
| III | Blood sugar | 0.120 | 0.140 | 0.120 |
| | Time in hours | .. | 4 | 2 |

TABLE VII.—PANCREATIC TRIAD.

The Figures Obtained on Dogs 9a and 10a.

| | | Normal. | Diabetes. |
|---|---|---|---|
| I | Blood sugar in per cent | 0.100 | 0.615 |
| II | Leukocytes | 6000 | 15,400 |
| III | Blood-coagulation time in seconds | 30 | 120 |

This diabetic dog had a spontaneous (not experimentally produced) diabetes in mild form. Not infrequently we observed on this dog polyphagia, polydipsia, polyuria, glucosuria, hyperglycemia and convulsions with loss of consciousness. The dog has lived in the laboratory for more than three years and has given birth to two litters of puppies; the first litter consisted of one puppy and the second of two; one of which died shortly after birth. The condition of the dog sometimes greatly improves on a suitable diet. This dog is still living in the laboratory.

The following are the figures obtained by E. Boldyreff from tests on men:

TABLE VIII.—PANCREATIC TRIAD IN MAN.

| | | Normal | 1 | 2 | 3* | 4† cases |
|---|---|---|---|---|---|---|
| I | Blood sugar in per cent | 0.100 | 0.330 | 0.150 | 0.129 | 1.62(!) |
| II | Leukocytes | 8000 | .. | .. | 18,000 | 28,000 |
| III | Blood-coagulation time in minutes | 2 | 3½ | 5½ | 7 | |

* After Glaser.[14]

† After Curtis.[12]

Up to this point in our discussion, we have presented data relating to pathologic conditions; but the members of our triad undergo parallel changes even in normal conditions during some physiologic processes.

Our experiments on dogs "outside of digestion," that is, in the absence of acid gastric secretion, have shown that the blood-sugar content, the blood-coagulation time and the number of leukocytes do not remain on the same level, but vary with marked regularity and uniformity. This appears to be in connection with the so-called "*periodical*" phenomena, starting in the digestive apparatus immediately at the close of digestion and continuing without interruption until digestion sets in again. The author has long ago established the fact that "outside of digestion" there is observed a "periodical" secretion of the pancreatic juice, and the periods of its secretion in dogs and in humans are thirty to fifty minutes ("periods of work"), with intervals of one to two hours ("periods of rest"). Fig. 1, 2 and 3. The existence of periodical activity in higher animals was confirmed in America by W. B. Cannon[8] and by A. J. Carlson.[9]

In the accompanying Figs. (1, 2 and 3) we present the "periodical" variations observed in the members of the triad.

The phenomena of "periodical leukocytosis" are presented in Fig. 2 and Fig. 3 and are described in detail elsewhere.

All the data in this article indicate that certain blood changes result from depriving the body of pancreatic juice, whether this loss occurs from pancreatic fistula, pancreatectomy, injury or disease.

But we have also made experiments of an opposite nature, in addition to our observations with absorption of periodically secreted pancreatic juice. We introduced zymogene pancreatic juice into the blood and examined the blood before and after this introduction. These data will soon be published in detail elsewhere. Here I will quote just one of numerous experiments relating to the effect produced on the number of leukocytes by the introduction of pancreatic juice into the blood. With large doses, the number of white blood cells quickly decreases, but later leukocytosis appears (Table IX).

Introduction of active pancreatic juice into the duodenum produces the same effect (Table X).

We have also made experiments with substances, such as atropin, inhibiting the pancreatic secretion, and drugs like pilocarpin and nicotin which excite this secretion. The data obtained were in general analogous to all preceding findings. These experiments will also be published in a separate article devoted to the mechanism of the leukocytosis.

We see a marked decrease in the number of leukocytes after the introduction of pancreatic juice into the blood. We have made 10 such experiments; the results were the same in each case. I began these experiments in 1914 at the University of Kazan in collaboration with Dr. Sokoloff.

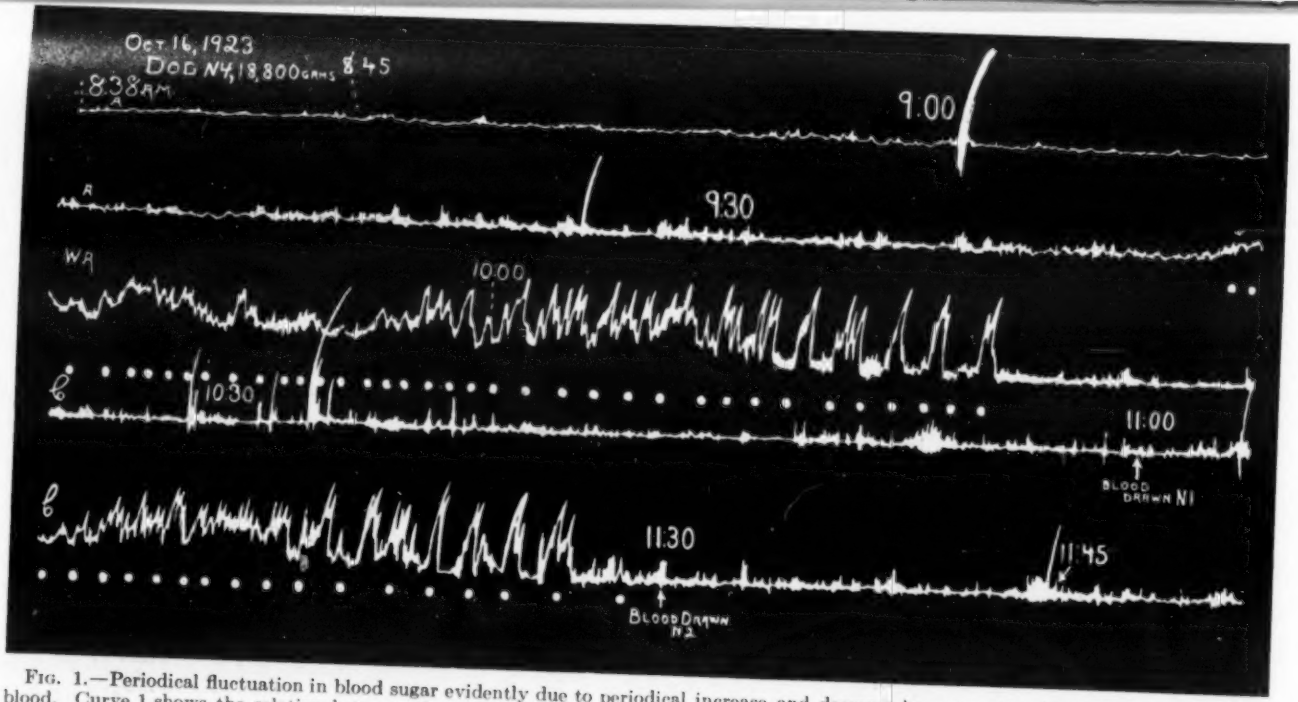


FIG. 1.—Periodical fluctuation in blood sugar evidently due to periodical increase and decrease in pancreatic glucolytic ferment in the blood. Curve 1 shows the relation between the manifestations of periodical activity of the digestive system outside of digestion and the changes of sugar content in the blood. It represents the record of periodical gastric contractions and periodical secretion of pancreatic juice (shown by dots) which occur simultaneously. Reaction in the stomach is indicated at the beginning of each line: (*a*) acid, (*b*) alkaline. The time marked every half hour. Blood sample No. 1 taken during the "period of rest" (absence of pancreatic secretion and gastric contractions) shows higher sugar, 0.094 per cent than sample No. 2 taken at the end of the "period of work" (during the secretion of pancreatic juice and gastric contractions), 0.075 per cent. Several experiments were made and similar results were obtained. The tracing is continuous from the left-hand top to the right-hand bottom. (Experiments on dog by E. Boldyreff.[2])

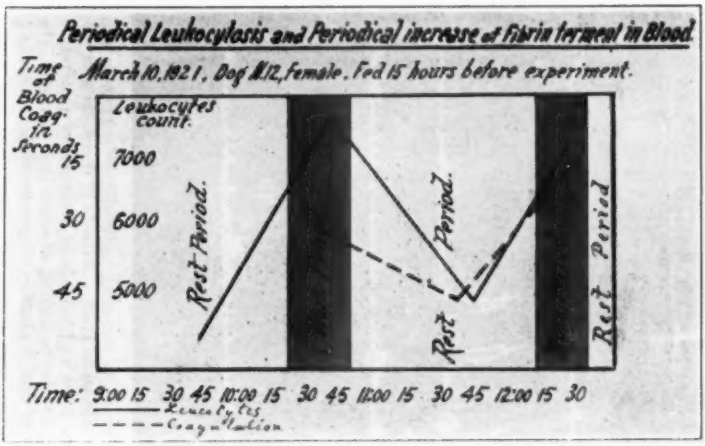


FIG. 2.—Periodical fluctuation in leukocytes number and blood coagulability. The periodical activity is presented here, but in a different manner from that on the Fig. 1. There the "periods of work" (third and fifth lines) and the "periods of rest" (rest of the lines) are shown just as they were registered on the kymograph during the experiment; while here both are shown schematically, but true to scale. Here we see that the first "period of rest" is somewhat longer than one hour and the first "period of work" (colored gray) slightly less than a half hour. Durations of the second "periods of work and rest" are about the same. The curves of the leukocytes and blood-coagulation rise during the "periods of work" and run practically parallel to each other.

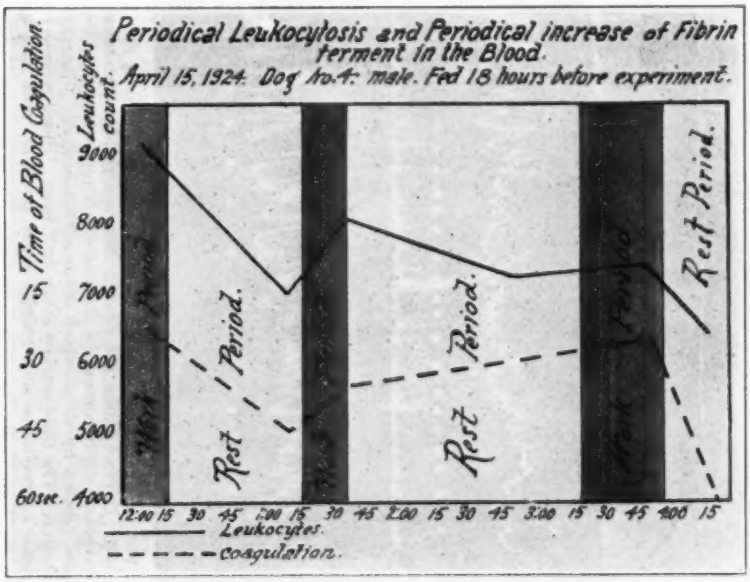


FIG. 3.—Periodical fluctuation in leukocytes number and blood coagulability. The same phenomena are presented as Fig. 2, but on a different dog. The experiment here was extended to include 3 "periods of work," and 3 "periods of rest."

The curves of leukocytes and blood coagulation similarly rise during "periods of work" and "periods of rest;" they also run almost parallel.

TABLE IX.—INTRODUCTION OF ZYMOGENE PANCREATIC JUICE INTO THE BLOOD.

(Dog No. 31. Pancreatic Fistula. Experiment by A. Boldyreff.)

| Time after operation in days | 1 | 2 | 4 | 5 Pancreatic-juice injected into blood 15 cc. | 5 50 minutes after introduction of juice | 5 2½ hours after introduction of juice |
|---|---|---|---|---|---|---|
| Leukocytes . . . . . | 13,400 | 9400 | 15,400 | 15,800 | 1500 | 5300 |
| Blood-coagulation time in seconds . . . . . | 75 | 45 | 45 | .. | 30 | |

TABLE X.—INTRODUCTION OF ACTIVE PANCREATIC JUICE INTO THE DUODENUM.

Dog. No. 7; weight 11,200 gm. Fed fourteen hours before experiment.
Fistulæ of duodenum and stomach. Stomach and duodenum empty.
Experiment by A. Boldyreff.

12.15 P.M. "Period of rest" 10,300 leukocytes.
12.32 P.M. Introduced into duodenum 75 cc. "periodical" active pancreatic juice at 40°C. Until 3.30 P.M. reaction in stomach remained alkaline.
12.45 P.M. . . . . 10,800 leukocytes
1.00 P.M. . . . . 7,400 leukocytes } "period of rest"
1.20 P.M. . . . . 7,600 leukocytes

We see that about half an hour after the introduction of the pancreatic juice into the duodenum the number of leukocytes was decreased by about 3000. Exactly the same experiments (in method and result) were performed eight times on two different dogs.

TABLE XI.—INTRODUCTION OF PANCREATIC JUICE INTO THE DUODENUM.

(Same dog as in Table X. The dog fasted throughout the experiment.)

| | | |
|---|---|---|
| III–31–24 | 10.27 A.M. "period of rest" . . . . . | 6800 leukocytes |
| | Introduction of pancreatic juice into the duodenum (moderate dose, about 50 cc.) | |
| | 5.00 P.M. "period of rest" . . . . . | 6000 leukocytes |
| IV– 2–24 | 10.09 A.M. "period of rest" . . . . . | 9400 leukocytes |
| | Introduction of pancreatic juice into duodenum (same dose) | |
| | 5.24 P.M. "period of rest" . . . . . | 7600 leukocytes |
| IV– 3–24 | 10.51 A.M. "period of rest" . . . . . | 9000 leukocytes |
| | Introduction of pancreatic juice (same dose) | |
| | 5.52 P.M. "period of rest" . . . . . | 6300 leukocytes |
| IV– 4–24 | 10.20 A.M. "period of rest" . . . . . | 8200 leukocytes |
| | Introduction of pancreatic juice (same dose) | |
| | 4.56 P.M. "period of rest" . . . . . | 5700 leukocytes |

This pancreatic juice in all cases produced a decrease in the number of leukocytes.

Thus it would appear from the foregoing experiments that the introduction of pancreatic juice directly into the blood or into the duodenum produces a marked decrease in the number of leukocytes.

It has been observed that sometimes the use of substances acting on some one member of the triad affects the other members as well. Thus, subcutaneous injections of 10 units of insulin in dogs produced leukocytosis and decreased the coagulability of the blood.

TABLE XII.—ACTION OF INSULIN ON LEUKOCYTES AND BLOOD COAGULABILITY IN DOGS.

(Experiments by E. Boldyreff.)

| | Normal | After insulin | Remarks |
|---|---|---|---|
| Leukocytes . . . | Dog 11a— 3,500<br>Dog 12a—11,000 | Dog 11a— 6,300<br>Dog 12a—20,200 | Such experiments were done on seven dogs, the results were identical in all cases. |
| Coagulability in seconds . . . . . | Dog 11a—35<br>Dog 12a—45 | Dog 11a—200<br>Dog 12a—130 | |

However, the appearance of these two members of the triad produced by the injection of insulin was of only short duration.

Here we see an example of the division of the members of the triad: after insulin the quantity of sugar in the blood decreases, but the coagulation time of the blood increases and the number of leukocytes augments.

As yet I refrain from analysing the causes of this phenomenon.

I would like to mention that Partos and Svec[10] have recently obtained results quite opposed to mine: they report that the coagulation time decreases with the increase of sugar. I would not attempt to judge why they came to such conclusions.

In the most recent American literature, we find confirmation of some of our data. For instance Allan[11] of the Mayo Clinic, and Joslin, Root and White[12] as well as Curtis and Dixson,[13] have found that in diabetes a pronounced leukocytosis is observed. Glaser[14] also reported our complete triad in diabetes mellitus in man.

In this discussion, I refer only to the two new factors—leukocytosis and change in blood coagulability—found in my latest experiments performed in collaboration with E. and A. Boldyreff. These two pathologic factors were always observed in injury of the pancreas parallel with the third phenomenon which has long been known, namely, an increase of blood sugar in these conditions. Therefore, I have given to this association of three permanent phenomena the name "Pancreatic Triad," anticipating that in the course of time it may be increased by the discovery of new members.

We do not consider the name "*Triad*" as a definitive term for the complexity of all the pathologic phenomena observed by us and other authors connected with the affection of the function of the pancreas. Their number may increase later. For instance, we know

that removal of the pancreas or injury to its function involves usually a disorder of general metabolism and sometimes that of the fat metabolism in particular.

As yet, we refrain from any theoretical explanation of the problem; we only desire to offer our experimental data on dogs which are also confirmed by our observations on men, though as yet not very numerous.

In a special report, we expect to illuminate this problem in detail, by our experimental data and observations, as well as by the data in the literature.

But even now we believe that our pathologic triad can be of great help to the clinician for purposes of diagnosis and prognosis. Thus, if all the members of the triad are present in a pronounced degree, the diagnosis of some pancreatic disturbance is certain. Furthermore, in the presence of the triad, operative intervention is likely to be followed by unfavorable results: poor wound healing is probable, and even gangrene is possible. At any rate we know that just these results are being observed after removal of the pancreatic gland or complete diversion of its secretion. And the triad testifies to a more or less complete exclusion of pancreatic juice from the organism.*

**Summary and Conclusions.** The pancreas is an organ so important and so necessary to the general metabolism that its removal produces very complex conditions of disease in the organism. Serious pancreatic lesions also result in a varied and complex pathology, often very confusing. In this problem experiments on animals are of great help. We can either remove the pancreas wholly or partially, either head, tail or body, or save the gland, removing the pancreatic juice partially or wholly through a fistula or fistulæ. Finally, we can introduce into the animal's body an excess of pancreatic juice.

Clinicians do not have exact knowledge of the state of the pancreas, in what degree or quality it is impaired, or how the pathologic phenomena observed by them depend on this injury. We physiologists examine the animal in health and then bring about various well-known, strictly definite pancreatic destructions; we follow the development of various pathologic processes, ensuing as the result of these injuries. We can make anatomic studies of the

* If the question arises whether some infection may be producing the appearance of leukocytosis in this triad, I should answer as follows: All infections have a period of incubation, and the development of leukocytosis due to an infection (for example, after an operation) requires a long time, not less than twenty-four hours. But some of our data are obtained on nonoperated animals, known to be healthy (except for diabetes), and human beings with diabetes.

Besides, as a rule, our data were observed a *short* time (one or two hours or a little more), after a certain operation, and before any infection could develop to affect the animal.

Finally the "periodical" variations in the members of our triad in absolutely healthy dogs, also observed after very short intervals (about an hour), speak against the possibility of infection.

animal at any time. Therefore, it is easier for the physiologist to determine the basic facts of the physiologic activity of the pancreas and those pathologic phenomena which result from its various diseased conditions. Of course, the clinical data are extremely valuable for physiology, and a collaboration of the two is especially fruitful.

Complete loss of pancreatic fluid, either by pancreatectomy or fistulæ, produces a "Pancreatic Triad" of: (1) a rise in the percentage of blood sugar; (2) a decrease of the blood coagulability; (3) the appearance of leukocytosis. This is a complex useful in understanding the physiology of the gland, but also in diagnosis and prognosis.

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## CLINICAL AND EXPERIMENTAL STUDIES ON CALCIUM AND CHOLESTEROL IN RELATION TO THE THYROID PARATHYROID APPARATUS.*

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The discovery of the active principle of the parathyroid gland by Collip[1] has recently given impetus to further experimental investi-

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gation into the physiology of these endocrine organs. Much has lately been added to our knowledge of their function, more especially in means of delaying and preventing fatal tetany which usually follows their extirpation. A very excellent review of the present status of the physiology of these glands has recently been published by Dragstedt.[2]

This work was attempted with the idea of utilizing one of the methods of preventing or controlling tetany after parathyroidectomy, in studying the relationship of the thyroid to the parathyroid. One of these methods outlined by Jones[3] required only preoperative administration of cod-liver oil, so that observation could be carried on without danger of results masked by treatment.

Sweet[4] has observed that some of the symptoms of severe hyperthyroidism, such as tremor, nervousness and hyperpyrexia are somewhat comparable to the symptoms ascribed to parathyroid deficiency. Sweet[4] also believes there is a definite relationship between calcium and cholesterol in the normal and pathologic animal and with these points in mind, the blood calcium and cholesterol were studied in the thyroparathyroidectomized dog and in patients with toxic thyroid disease.

Because of the close anatomic relationship between the parathyroid and thyroid glands, and because of their embryologic association, there may possibly be some physiologic connection between the two glands in thyroid disease. Gley[5] advanced the theory that the parathyroids were embryonic thyroid tissue and introduced evidence which has not been convincing. Foster[6] states that there is not a vestige of scientific evidence of the correlation of these glands.

**Embryology.** The parathyroid glands are epithelial bodies arising from the dorsal diverticula of the third and fourth pharyngeal pouches.

Two pairs of these bodies are formed and as they move caudad and as the ducts of the pharyngeal pouches atrophy they are set free and lie in close anatomic relationship with the thyroid gland. The pair arising from the third pouches lie, in the adult, one on each side of the inferior portion of the thyroid somewhat medially and frequently become embedded in the thyroid tissue. The pair arising from the fourth pouches are located on each side of the superior portion of the thyroid somewhat laterally and usually are outside the thyroid tissue.

The solid epithelial bodies become broken up into masses and cords of polygonal entodermal cells intermingled with bloodvessels. In postfetal life lumina appear in the cell masses and fill with a colloid material which is somewhat similar to, but not to be related to thyroid colloid material.[2]

The thyroid develops from three anlagen, a median and a pair of lateral outgrowths from the primitive pharynx. The median anlage comes from the floor of the pharynx, its site of origin being marked

in the adult by the foramen cecum of the tongue. It forms the isthmus and pyramidal lobe of the definitive thyroid. The lateral anlagen grow down from the ventral border of the fourth pharyngeal pouches and form the lateral lobes of the gland. The parathyroid glands are in close anatomic relationship with these lateral lobes in the adult.

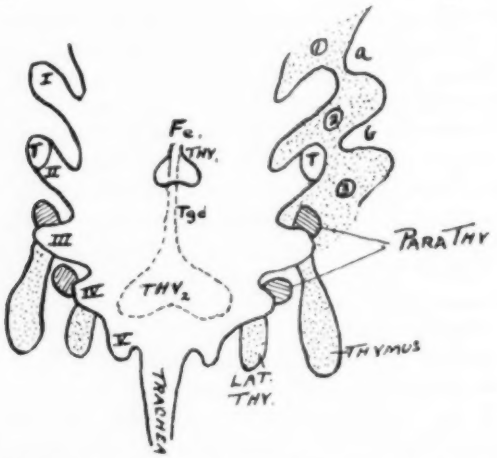


CHART I.—Diagram of pharynx of human embryo, showing the origins of the anlages of the thymus, thyroid and parathyroid (epithelial bodies). *Thy*$_1$, earliest position of thyroid anlage; *Thy*$_2$, secondary position of thyroid anlage; *Tgd*, thyroglossal duct; *Fc*, foramen cecum; *Lat. Thy*, lateral thyroid anlages; *Para Thy*, parathyroid bodies; *T*, tonsil; *I*, *II*, *III*, *IV*, *V*, pharyngeal pouches; *a*, *b*, first and second branchial grooves (gill clefts); *1*, *2*, *3*, first, second and third aortic arches in the cores of the branchial arches. (After Kohn.)

**Histology.** The epithelial cells of the parathyroid are of two chief types, the principal, and the oxyphil or acidophil cells.[7]

The principal cells are ovoid or polygonal with a clear cytoplasm and a large deeply staining spherical nucleus. The acidophil cells are less abundant and of similar shape, containing a small central spherical nucleus rich in chromatin and a deeply staining granular cytoplasm.

The cells are arranged in solid epithelial masses or cords and occasionally the cells surround a central lumen which is filled with an acidophil substance resembling colloid.

The connective tissue of the gland is variable, usually forming a thin distinct capsule and occasional trabeculæ.

The blood supply of the parathyroid is very rich, indicating the activity of the gland.

**Anatomy.** The anatomic distribution of the glands varies to a great extent in the same species and to an even greater extent in different species.[8] In man they are usually four in number, the superior pair lying close to the thyroid but not commonly within

the thyroid tissue, in the middle third of its posterior border approximately at the level of the cricoid cartilage.

The inferior pair ordinarily lies behind the lower third of the thyroid on a plane anterior to the recurrent laryngeal nerve and in close relationship to and usually anterior to the lower branches of the inferior thyroid artery.[9] These are often found to be embedded in the thyroid tissue.

There have been found accessory parathyroids in various positions along the anlage route; sometimes embedded in the thymus or thyroid tissue. It is to the presence of these accessory glands that failure to produce fatal tetany in dogs after thyroparathyroidectomy has been ascribed.

In the light of recent work we are of the opinion that fatal tetany does not always occur in the usual time limits and that accessory parathyroids are not a common finding.

**Surgical Significance.** The importance of the parathyroid bodies was first determined some years ago by the results obtained when the thyroid gland was removed, and this is still the chief surgical significance. The occurrence of fatal tetany after total excision of the thyroid in some patients led to the discovery of these small bodies in the thyroid gland. They are now carefully preserved in operations for removal of a diseased thyroid. Cases have been reported, however, in which tetany occurred, although the parathyroids were apparently not touched. Such a case is here later reported in which the parathyroids were not thought to be disturbed although tetany occurred. This perhaps may be suggestive of a balance between the thyroid and the parathyroid.

The function of the parathyroids is unknown and although it is usually suspected that there is a relationship with other endocrine organs, what this relationship is, has yet to be determined. There is, however, a definite relationship between the parathyroids and calcium metabolism as evidenced by the fact that extirpation of the glands is usually followed by a distinct fall in blood calcium. Further evidence is given by the fact that the recently discovered active principle of the gland[1] when injected into normal animals causes a rise of blood calcium, and prevents the usual fall in blood calcium in parathyroidectomized dogs.

The occurrence of parathyroid tetany has been ascribed to lowered blood calcium alone, but evidence is now accumulating which may point to another explanation, the calcium change being an effect rather than a cause.[1, 3, 15, 17, 26]

Another theory for the cause of tetany considered by Dragstedt[2] and Greenwald[10] and others is that of intoxication. The prevention of tetany by bleeding and infusion of salt solution, and by intravenous calcium-free Ringer's solution[15] is suggestive of a dilution of toxic products in the blood stream and consequent control of tetany. Search has been made for toxic substances in the blood of para-

thyroidectomized animals without success. Guanidin was suspected as a possible cause of intoxication,[11] but was not found consistently in increased amounts in the blood of parathyroidectomized animals.[10] Guanidin poisoning is also not identical with parathyroid tetany.[12]

**Parathyroid Tetany.** When the parathyroid glands are completely removed from a dog, in about 90 per cent of cases,[12] there follows, after a symptom-free period of 2 to 5 days, the beginning symptoms of *tetania parathyreopriva*. These symptoms are first noticed as increased restlessness, loss of appetite and slight incoördination of gait, especially in the hind legs. Greenwald[13] states that one of the first symptoms he notices is apparent headache, the dog rubbing its head against the sides of the cage and appreciating massage of the head.

Very soon after these symptoms have appeared one may feel fibrillary twitching of all of the muscles of the body, especially those of the hind legs and of the jaws. Later coarse tremors develop followed by increasing spastic contractions. The respirations are increased, salivation is profuse and the animal goes into long periods of spasticity with occasional clonic contractures of the leg muscles. If the attack of tetany lasts long enough to prevent respiratory movements, the animal dies. He may, however, have several attacks from which he recovers completely until a succeeding severe attack is fatal.

The occurrence of the tetany varies greatly in time of onset, severity and syndrome. It occurs with marked regularity, however, and various observers have stated that failure to produce fatal tetany after parathyroidectomy indicates technical failure to remove all the parathyroid tissue or indicates the presence of aberrant gland tissue.

It is a well-conceded fact that after parathyroidectomy there is a disturbance of calcium metabolism, so that there is a fall of blood calcium from a normal of 9 or 10 mg. per 100 cc. to 5 or 6 mg. per 100 cc. after 3 to 4 days. This observation suggests one of the theories of the origin and cause of parathyroid tetany. The adherents of the theory claim that the lowered calcium content of the blood is responsible for the fatal tetany. Further evidence is given by the increase in blood-calcium level following administration of the active principle of the parathyroid gland.[1] Greenwald[14] has shown that calcium excretion is not increased after parathyroidectomy.

It is evident, however, that tetany can not be explained solely on a calcium deficiency basis, nor can the theory that tetany is due to an intoxication be accepted without further evidence.

**Methods of Controlling and Preventing Tetany after Parathyroidectomy.** Since Luckhardt and Rosenbloom[15] and Dragstedt[16] reported that tetany could be prevented in parathyroidectomized animals, several methods have been shown to be effective in preventing

death in these animals for periods of months to two years. None of these methods of controlling tetany are based upon any one principle. It seems to be true that if a parathyroidectomized animal is carried over the critical period, especially the second and third weeks after operation, by any one of these methods, it may live for long period of time with little or no treatment, only to be thrown into a severe or moderate attack by some apparent indirect influence, such as meat diet, estrus or pregnancy. It seems quite probable that in a large number of dogs undergoing parathyroidectomy, there would be a few that could withstand this critical period without fatal tetany. In the experience of men who have done this work, there are always a few dogs who do not show the characteristic symptoms in the usual 2 to 5 days. These have hitherto been considered failures in removing the parathyroid tissue or as indicating aberrant parathyroid glands. Very likely these dogs were imbued with whatever is necessary to withstand the critical period and live on just as the dogs who receive specific preoperative or postoperative treatment.

Luckhardt and Rosenbloom[15] found that slow intravenous injections of Ringer's solution controlled and prevented tetany in parathyroidectomized dogs. Dragstedt and Peacock[17] found that parathyroidectomized dogs placed on a meat-free diet did not develop tetany if administered lactose and milk in large quantities. Inonye[18] corroborated this and found galactose also effective.

Oral administration of calcium lactate[19, 20] and a combination of milk diet and intravenous injections of calcium chlorid[21] were also effective.

Other methods of preventing tetany are oral administration of ammonium chlorid; [22, 23] magnesium chlorid;[24] magnesium lactate[25] and strontium lactate.[20, 26, 27]

Dragstedt[26] found that kaolin when administered by mouth kept parathyroidectomized dogs alive.

All of the above methods of preventing tetany are by means of postoperative therapeusis and indicate a control of the apparently abrupt change which occurs during the critical period, and which usually ends in fatal tetany. Some of these workers report that after a period of time varying from 6 to 8 weeks, the dogs became apparently normal, and were able to do without treatment and resume normal diets, even though the blood calcium remained at a low level. It is not unusual for these dogs to develop tetany late, brought on by pregnancy or lactation or by some unapparent cause. This also seems to hold true clinically in man. A woman was admitted to the New York Hospital with symptoms of gallbladder disease. She had two years previously undergone a thyroidectomy for a toxic adenoma of the thyroid. Three days after this operation she developed signs of parathyroid deficiency, with one attack of tetany. She recovered completely and had no further

symptoms. The patient was again operated upon two years after the thyroidectomy and a gall bladder full of stones was removed. Three days postoperative she again suffered two attacks of quite severe tetany. She then recovered completely and has had no further symptoms.

Lately Brougher[28] has reported that postoperative administration of cod-liver oil and yeast delayed the onset of tetany and ameliorated its severity in parathyroidectomized dogs. He also reported that this treatment raised the blood calcium to normal. Buchbinder and Kern[29] have also reported that tetany is delayed after parathyroidectomy in jaundiced dogs.

The methods of preventing parathyroid tetany described above, all require postoperative treatment. In contrast to these is one requiring only preoperative treatment: Jones[3] reported that the administration of cod-liver oil before the removal of the parathyroids is also effective in lengthening the lives of the parathyroidectomized dogs and in preventing tetany.

Our present experiments aim to repeat Jones' work, and, if successful, to study the calcium and cholesterol in the experimental animals and determine, if possible, their relationship.

Sweet,[4] is of the opinion that calcium and cholesterol go hand in hand in metabolism and in his work on gall bladders[34] he found a definite change in the cholesterol content of the blood before and after cholecystectomy. If there is such a definite change in calcium metabolism in parathyroid deficiency, it is his opinion that there would also be a change in cholesterol metabolism, which if established might help to throw some light on the subject of the pathogenesis of parathyroid tetany. An example of the apparent association between these two substances is seen in acute nephrosis where there is found a disturbance of calcium and cholesterol in the blood, which is not explained entirely on the basis of retained blood substances. There may be a balance of some kind between calcium and cholesterol, such as might be explained by a mutually protective colloid mechanism. A disturbance of the balance might account for symptoms not explained by changed blood values above.

I have repeated Jones' work and found that cod-liver oil, when administered in doses of 20 to 50 cc. daily over a period of 2 to 3 weeks before operation prolongs the life of the thyroparathyroidectomized dog, delays fatal tetany and diminishes the severity of tetany when it does occur. The blood-calcium level drops as in untreated animals, reaching a lower level. Tetany was observed in 71 per cent of the treated dogs and it is not certain that it was absent in the other dogs. This work, therefore, does not confirm Jones' statement[3] that this treatment prevents tetany. Greenwald[30] has also been unable to prevent tetany by the use of cod-liver oil as reported by Jones. All of the animals of this series died, one living 142 days after the operation.

**Experimental Work.** Dogs of any type were used as experimental animals, no selection being made as to age, size or sex. Five dogs were used as controls and 7 treated with cod-liver oil.

In all cases the thyroid was removed together with the parathyroid, care being taken to remove tissue immediately adjacent to the thyroid posteriorly. If the calcium level falls as usual[2] with the above technique, it seems logical to suppose all the parathyroid tissue removed, even without fatal tetany in 2 to 5 days. In only one case did the calcium level fail to fall as in the other dogs of this series, and this was taken to indicate failure of removal of all of the parathyroid tissue.

Several of the thyroids removed in this series were sectioned by Dr. José F. Nonidez, of the Department of Anatomy at Cornell University, and two parathyroids were found in each lobe. In all of these cases sectioned the parathyroids were embedded in the thyroid or closely associated with it under its capsule, so that complete extirpation of the thyroids in the majority of cases, and possibly all cases, assumes removal of all parathyroid tissue.

The control dogs were fed, *ad lib.*, the usual kennel diet, which consisted of bread, meat, table scraps and dog biscuit. No attempt was made to control the diet. It is quite evident that a dog cannot eat enough calcium or other material in a mixed diet such as this, to prevent the occurrence of tetany. The cod-liver-oil-treated dogs were also fed the usual kennel diet before and after operation, with the exception of Dogs 2 and 3 to whom a bread and milk diet was given after operation for one week. This seemed to have no effect on tetany appearance, so no further attempt was made to keep the dogs on milk or meat-free diet. Dog 1 ate this diet, including meat, daily, after operation until the day of occurrence of fatal tetany. All of the control and treated dogs recovered immediately after operation and showed no symptoms until the second or third day, when some refused food and became listless, and somewhat spastic. These symptoms increased slowly or rapidly, depending upon the number of days the animal lived.

The cod-liver oil was fed by stomach tube, daily. The dogs soon became accustomed to the tube and made no remonstrance to its introduction. Twenty cubic centimeters daily over a period of two weeks seemed to be adequate dosage and evidently optimal, for when the dosage was increased to 35 cc. for 42 days or 50 cc. for 30 days, no change in effect was noted and these dogs did not live as long as those treated with 20 cc. for 14 days. Dog 1, who lived the longest of the series, 142 days, received 20 cc. daily for 14 days before operation.

Blood samples were taken frequently and approximately at the same hour of the day, from the jugular vein. Calcium and cholesterol determinations were made on each sample.

From the accompanying chart (Chart II), it will be noted that

CHART II.—EFFECT OF COD-LIVER OIL ON THE TETANY OF PARATHYROIDECTOMIZED DOGS.

*Controls.*

| No. | Sex. | Weight in kilos. | Age. | Treatment. | Diet. | Appearance of tetany, days after operation. | Died. | Lowest calcium, mg. per 100 cc.—day of occurrence. |
|---|---|---|---|---|---|---|---|---|
| 19 | F. | 6.0 | Old | None | Usual | 31st and 32d | 35th p.o. day | 4.2; 10th p.o. day. |
| 20 | M. | 6.0 | Old | None | Usual | 11th and 17th | 23d p.o. day | 5.4; 17th p.o. day. |
| 12 | M. | 12.0 | Old | None | Usual | Tremors on 7th and 10th | 18th p.o. day | 4.4; 16th p.o. day. |
| 22 | F. | 2.0 | Old | None | Usual | 3d | 4th p.o. day | 8.7; 2d p.o. day. |
| 9 | M. | 6.5 | Old | None | Usual | 2d | 3d p.o. day | 7.1; 1st p.o. day. |

*Cod-liver-oil Treated Dogs.*

| | | | | Preoperative cod-liver oil. | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | M. | 3.0 | Old | 20 cc. daily, 2 weeks | Usual | 121st and 141st | 142d p.o. day | 5.4; 142d p.o. day. |
| 3 | F. | 2.8 | Young | 20 cc. daily, 2 weeks | Milk diet for 1 week p.o. | 15th and 20th | 32d p.o. day | 4.1; 15th p.o. day. |
| 10 | M. | 14.0 | Old | 35 cc. daily, 24 days | Usual | 19th; died in tetany | 22d p.o. day | 4.4; 3d and 16th p.o. days. |
| 2 | M. | 3.6 | Young | 20 cc. daily, 18 days | Milk diet for 1 week p.o. | None observed | 17th p.o. day | 5.4; 7th p.o. day. |
| 11 | F. | 8.0 | Young | 35 cc. daily, 47 days | Usual | 3d and 9th | 11th p.o. day | 6.0; 11th p.o. day. |
| 15 | M. | 9.0 | Young | 50 cc. daily, 30 days | Usual | 10th | 13th p.o. day | 6.0; 10th p.o. day. |
| 17 | F. | 6.4 | Young | 50 cc. daily, 26 days | Usual | None observed | Killed 59th p.o. day | 5.6; 10th p.o. day. |

the treated animals lived longer than the control animals. The average length of life of the controls was 16.6 days and the average length of life of the treated animals was 42.3 days. It will be noted that all of the control dogs were "old," and that two, 19 and 20, lived 23 and 35 days. The calcium level fell as usual in these two dogs (see Charts VIII and IX). The symptoms were the usual ones seen in parathyroidectomized animals. Both animals died in tetany. This is taken to mean that these dogs were endowed with whatever material is necessary to delay fatal tetany.

Tetany appeared later in the treated animals, the average time of onset being at 35.6 days, while in the control dogs the average time of onset was at 10.8 days. Tetany was observed in all of the control animals and in all but two of the treated animals. In this respect only does this work differ from Jones in his report[3] on the action of cod-liver oil on thyroparathyroidectomized dogs. Tetany was observed in 5 of the 7 treated dogs and the dogs were not observed closely enough to state that tetany did not occur in the other 2, but it is possible that they developed tetany as did those observed.

The tetany in the treated dogs was less severe than in the control dogs. In most cases the dogs became very emaciated after continued refusal of food and water, and this was borne out by autopsy.

Dog 1 lived the longest of this series, 142 days. This dog seemed exceptionally free from all symptoms, except for slight clumsiness of gait until the 121st postoperative day, when he suddenly developed tetany (Chart VI). He recovered from this in a few hours and was not observed to have further symptoms until the day of his second attack which proved fatal. This seems to indicate that an animal can live without parathyroid tissue and when carried over the critical period by some method, unexplained, will live indefinitely, but may at any time be subject to a return of tetany which may be fatal. The cause of this recurrence is unknown.

There is no evidence that other endocrine organs take over the function of the parathyroids when the glands are removed. All of these dogs were carefully autopsied and all of the endocrine organs of several animals were examined microscopically. The only persistent finding was a definite atrophy of the spleen to one-third to one-half its normal size. This may be explained by the fact that most of the dogs were greatly emaciated before death. In one dog (19) the pancreas was found to be granular, somewhat similar to a pancreas following ligation of the pancreatic ducts. On section, this proved to be a fibrosis of the gland with little normal tissue. One dog (1) showed a peculiar superficial ulceration of the gastric mucosa on the summits of the rugæ, with evidence of thrombosis of the vessels of the mucosa.

No changes were found in the thymus, suprarenals, testes, ovaries, or pituitary glands. All of the dogs who died slowly in emaciation

showed colons filled with impacted feces. No changes could be made out grossly in the liver or gall bladders.

Careful search for accessory or missed parathyroids was made in each dog and none found, although suspicious gross tissue was sectioned.

**Blood Examination.** As explained above, calcium and cholesterol determinations of the blood were made at intervals before and after operation. The author is greatly indebted to Dr. Nellis B. Foster for the blood chemistry work on this problem. This work was done in Dr. Foster's laboratory in The New York Hospital by his assistants. Calcium determinations were made according to Clark and Collip's modification of Tisdall's method[31] and cholesterol determinations were done according to Bloor's modified method.[32]

The "normal" calcium and cholesterol determinations were made on 12 normal dogs. These were all within close range of the average which was found to be 9.9 mg. of calcium per 100 cc. of serum and 160 mg. of cholesterol per 100 cc. of blood.

There was a quite definite relationship between the calcium and cholesterol findings in both the treated and control dogs. This is evidenced by the fact that in most cases when the calcium-level fell, the cholesterol level rose, and *vice versa*. This was most marked when symptoms of tetany appeared.

This is illustrated by the accompanying chart of Dog 11, who was treated with 35 cc. of cod-liver oil daily for 42 days before operation. At first, under the cod-liver oil treatment, there was a slight rise in the calcium and a coincident, more marked, cholesterol rise. Before operation there was a marked rise in calcium for the first time, the cholesterol decreasing at the same time. After operation there was a fall in cholesterol and a fall in calcium upon the first determination. But upon the first attack of tetany, the cholesterol rose sharply, although there was only a slight fall in calcium. At the time of onset of the second attack of tetany there was again the rise in cholesterol with a fall in calcium. This has been a common finding that in most cases of severe tremors and actual tetanic convulsive seizures, the cholesterol rose about as frequently as the calcium fell, and usually there was a greater proportionate change in cholesterol than in calcium. This is well illustrated by the accompanying charts. Dog 11 had no signs of tetany with a calcium of 8.5 mg. per 100 cc. while the cholesterol was at a low level. On the appearance of tetany the calcium was 8.2 mg. per 100 cc., but the cholesterol determination had risen sharply to 230 mg. per 100 cc. On the occurrence of the second attack, the cholesterol rose to a still higher level of 260 mg. per 100 cc. while the calcium fell to 6.1 mg. per 100 cc. On the following days before death, no tetany was evident although the calcium level continued to fall. Determinations of cholesterol taken at this time showed a fall.

In 13 determinations made on blood withdrawn during a con-

vulsion, the average calcium finding was 5.7 mg. per 100 cc., while the cholesterol finding was 222 mg. per 100 cc. The "normal" calcium was 9.9 and the "normal" cholesterol was 160, so that the rise in cholesterol seems to be as marked and significant as the fall in calcium.

Eight of the 13 cholesterol determinations made while the animal was in convulsions, gave the highest value obtained on the dog. Six of these 13 calcium determinations gave the lowest findings obtained. Many of the dogs were free from convulsions with the

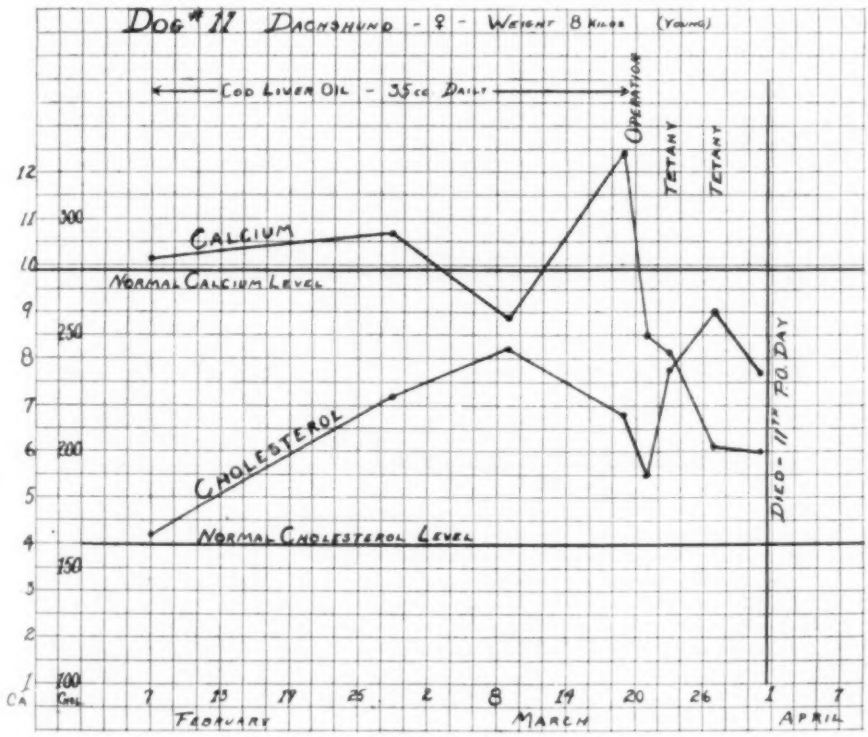


CHART III.

calcium at a "tetany" level, but in most cases the cholesterol was low. On the occurrence of tetany there would be little change in calcium but a definite change in cholesterol. In this series, throughout, there seems to be a relationship between the calcium and cholesterol performances. When the relationship was disturbed in some way, symptoms appeared.

There seems to be a more definite cholesterol change in the untreated dogs than in those treated with cod-liver oil. It was thought that perhaps the rise in blood cholesterol indicated a loss

of tissue cholesterol, and that the cholesterol content of cod-liver oil, which is 0.4 per cent, might be the explanation for the alleviation of tetany symptoms. In this connection, one dog was fed an egg diet containing 0.48 per cent cholesterol. After thyroparathyroidectomy this dog died in tetany just as the control dogs and no change in blood chemistry from the usual findings after operation was evident.

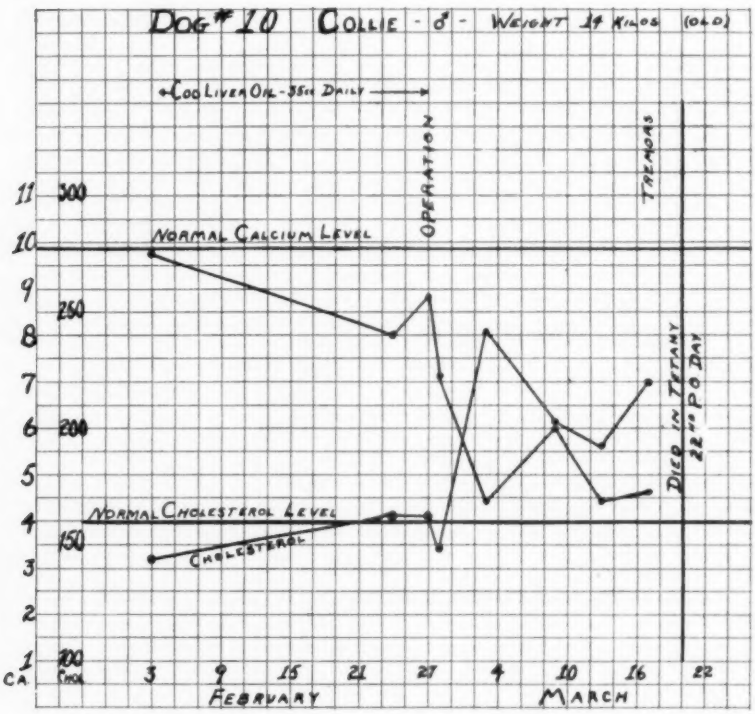


CHART IV.

McCarrison[35] states that the beneficial factor in cod-liver oil in the treatment of some of his thyroid patients may be due to its high iodin content. If this were true it might be inferred that cod-liver-oil treatment may be comparable to the administration of Lugol's solution. However, iodin is present in cod-liver oil in almost negligible quantities, 1 part in 5000. The iodin index and the iodin content are not to be confused.

Dog 10 further illustrates the relationship of calcium and cholesterol, although on the fifth day postoperative, when the calcium reached its lowest level and the cholesterol its highest level, no tetany appeared.

Dog 3, as shown on the chart, showed this condition quite clearly. On the day of first appearance of tremors, the cholesterol had his to its highest point and the calcium had fallen to its lowest point. Three days later, convulsions occurred but no blood samples were taken. The dog then recovered, apparently completely, and cholesterol taken 5 days after the convulsion showed a raised calcium and a very low cholesterol. Five days later a second tetanic attack occurred with the usual findings, that is, lowered calcium and increased cholesterol.

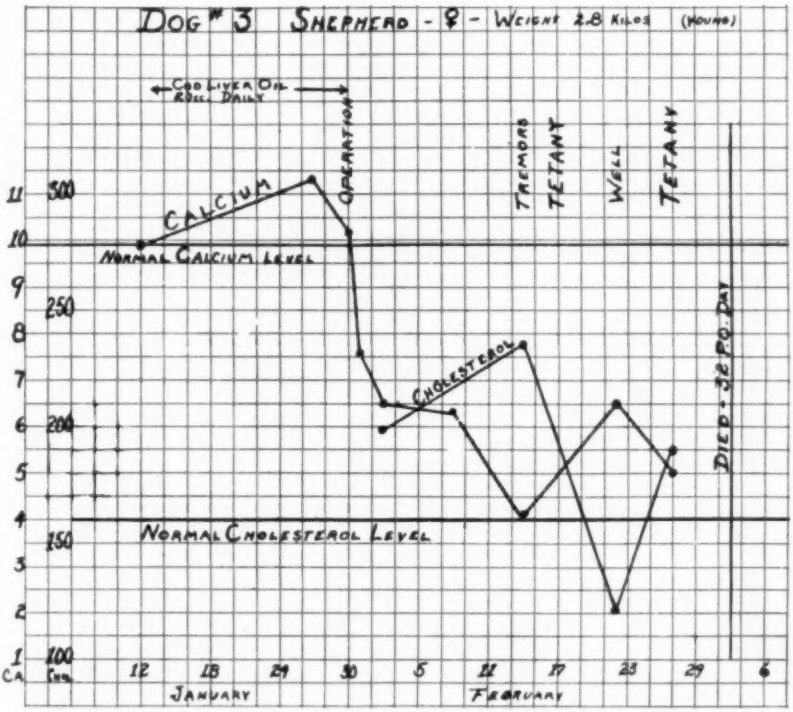


CHART V.

Dog 1 is especially interesting and bears out the finding of the importance of cholesterol in this experiment. This dog showed no symptoms whatever after operation, and calcium determinations taken at intervals showed a definitely lowered calcium and an insignificant rise in cholesterol. With the development of a sudden convulsive tetany, blood taken during the convulsion showed a slightly lowered calcium but a sharp and significant rise in cholesterol. The dog recovered thereafter, the cholesterol falling sharply. On the occasion of his second and fatal attack of tetany, the calcium value

fell to 5.5 mg. per 100 cc. and the cholesterol rose sharply to its highest point, 242 mg. per 100 cc.

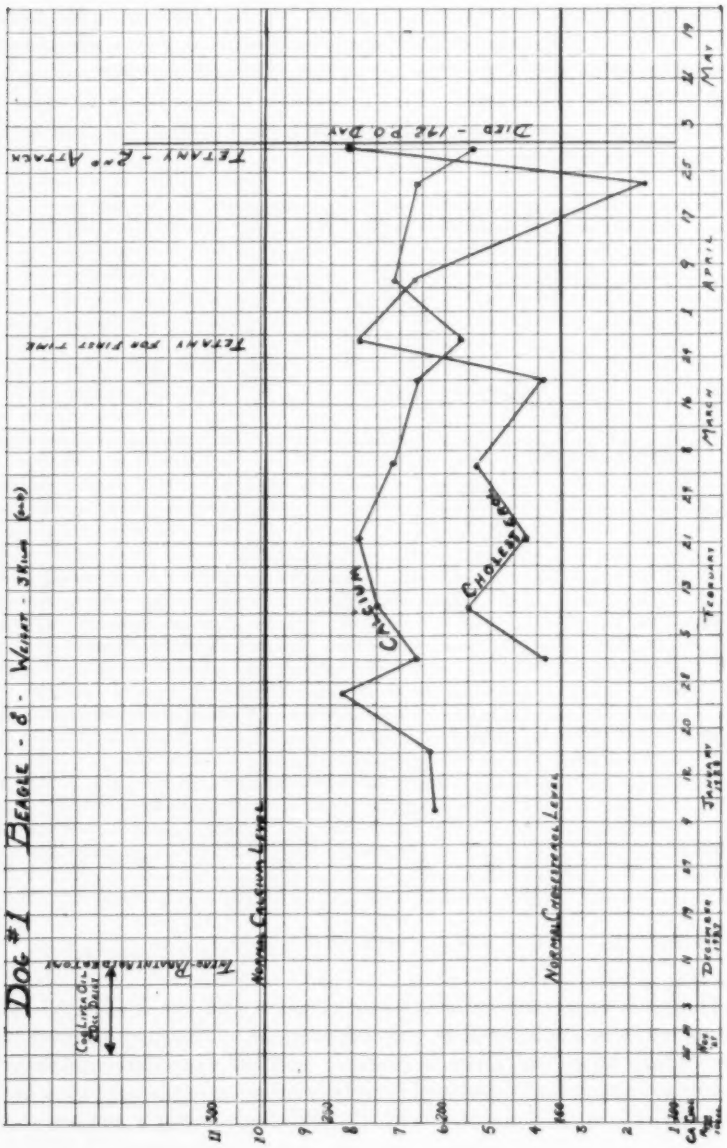


Chart VI.

It seems apparent that the dog was without symptoms with a low calcium, but as soon as tetany occurred, the cholesterol showed a

very decided rise while the calcium varied only slightly. This occurrence on two occasions with a reversal of the cholesterol curve between attacks seems significant of some relationship between cholesterol metabolism and tetany.

The same relationship was found to hold true in the control dogs, with an even more marked cholesterol change than in the treated dogs.

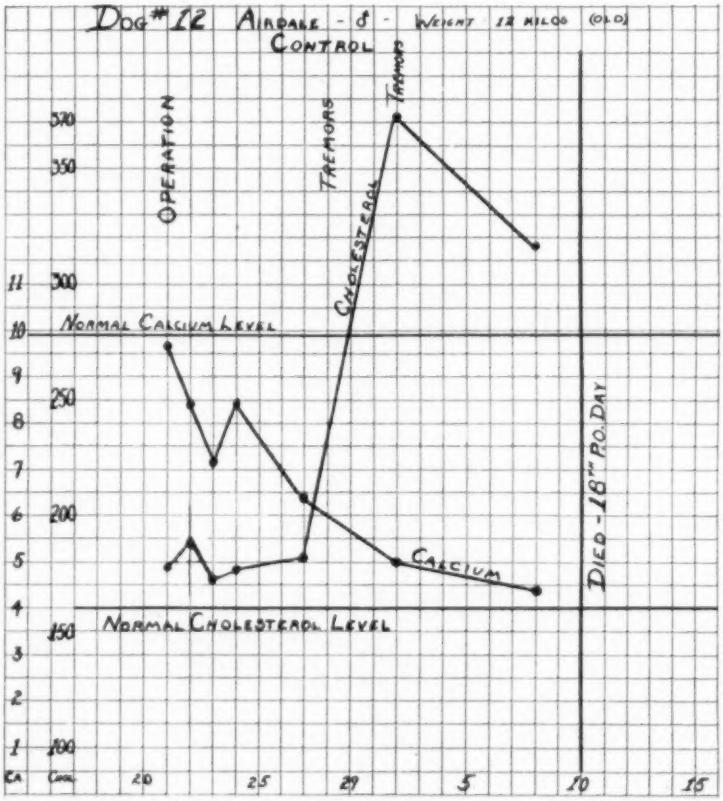


Chart VII.

Dog 12 showed tremors on the seventh and tenth days after operation, and examination of the blood showed a sharp rise in cholesterol. Later determinations during relief from symptoms showed a lowered cholesterol although the calcium level was still low.

Dog 19 bears out this theory more clearly. On the occasion of the lowest calcium value on the tenth postoperative day there were no symptoms, the cholesterol being at a low level. During the time the cholesterol hovered about the average normal, no tetany

appeared; but on the first appearance of tetany there was a decided rise in cholesterol with only a slight decrease in calcium.

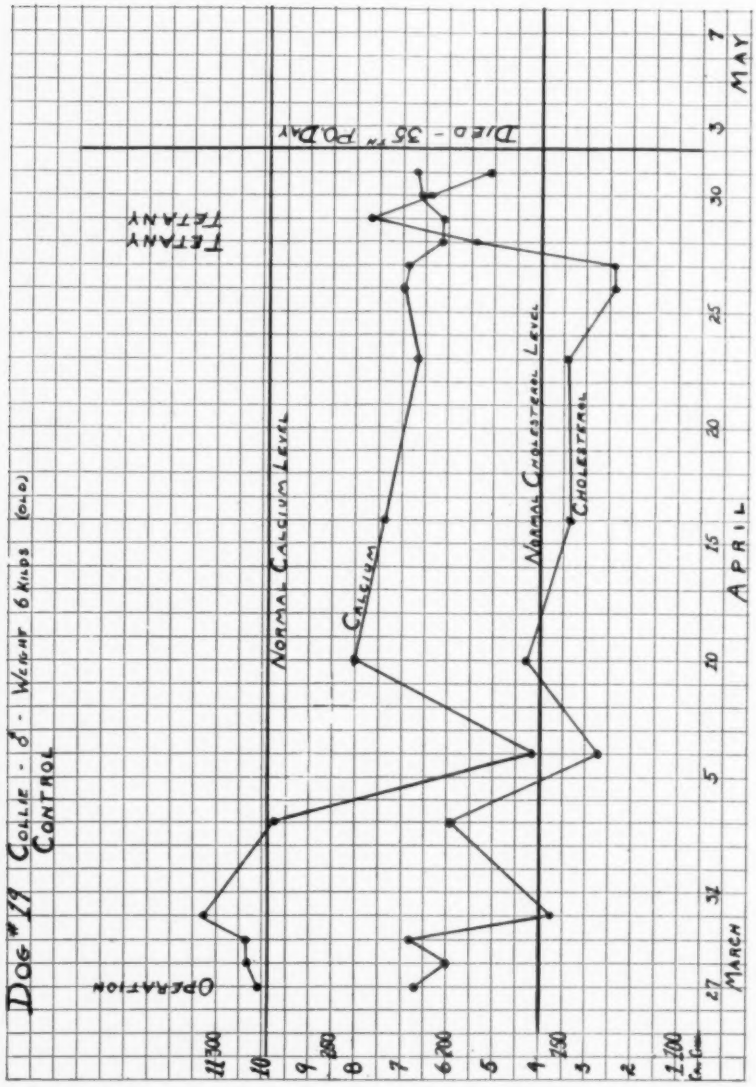


Chart VIII.

Dog 20 is the one exception we have found where the calcium and cholesterol curves moved in a like manner. We have no explanation for this fact that during the second attack of tetany the cholesterol fell to a normal level, although the calcium level lowered as usual.

Further evidence of the importance of cholesterol in this condition is shown in the chart of Dog 13, who was fed freshly ground thyroid material taken from Graves' disease patients at operation. In this dog the cholesterol rose as the calcium fell after continued feeding of the thyroids. After a short period of normal diet the curves returned to normal.

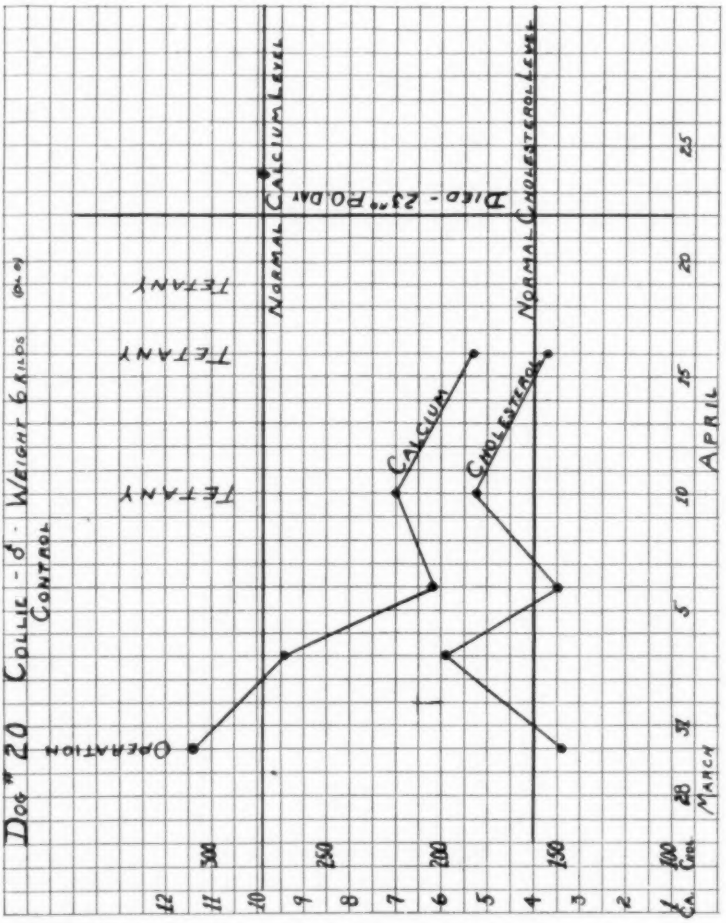


Chart IX.

It is interesting to note that Dog 1 lived with a definitely low blood calcium without symptoms for 142 days when tetany occurred. His skeleton was Roentgen-rayed at various times throughout the experiment and after death the bones were again Roentgen-rayed and examined, but no evidence of loss of calcium was found. He was also allowed to jump from a high table shortly before his death with no injury to the bones of his legs.

Ross[33] has recently reported that after prolonged low blood calcium the calcium content of the bone is diminished and that fractures of these bones heal slowly. Within the limits of these experi-

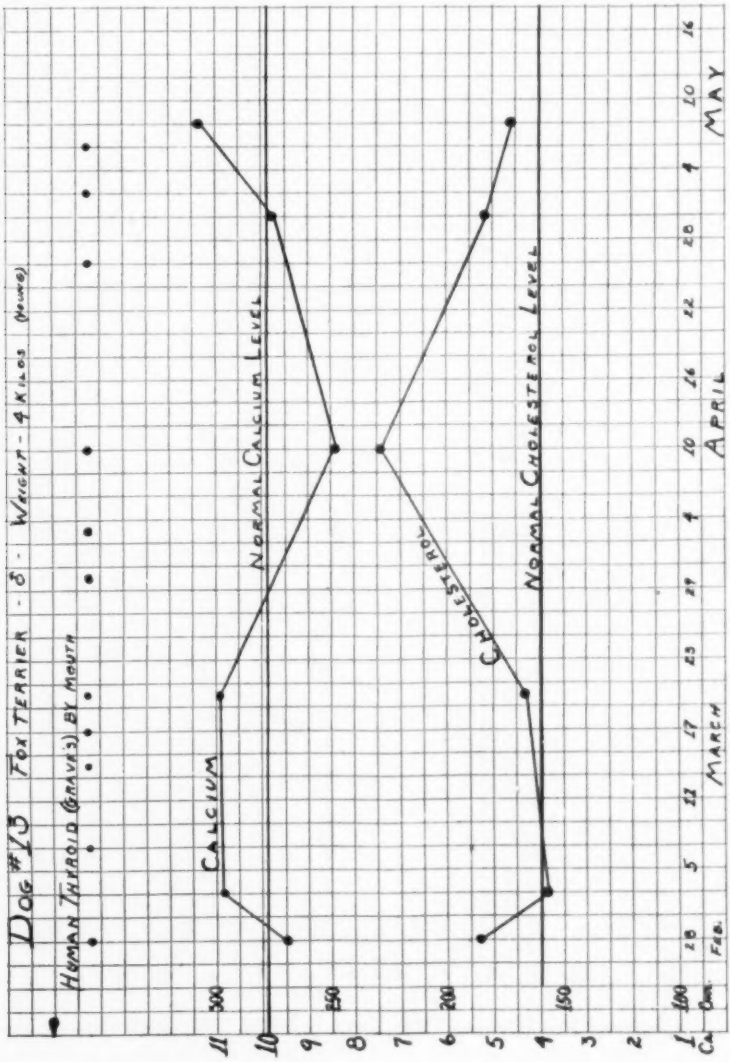


CHART X.

ments there was found no direct relationship between the prolonged low blood calcium and the calcium content of the bones.

From the above experiments it is here concluded that after thyroparathyroidectomy in dogs there follows a rise in blood cholesterol which is about as consistent as the fall in blood calcium. The change

in cholesterol seems to be more marked than the change in calcium and seems to be more apparent in untreated dogs than in those having had cod-liver oil before operation.

**Clinical Studies.** In view of the findings of the experimental work, we have made calcium and cholesterol determinations on patients with diseased thyroids. Eleven patients were studied, all of whom had exophthalmic goiters or toxic adenomas of the thyroid.

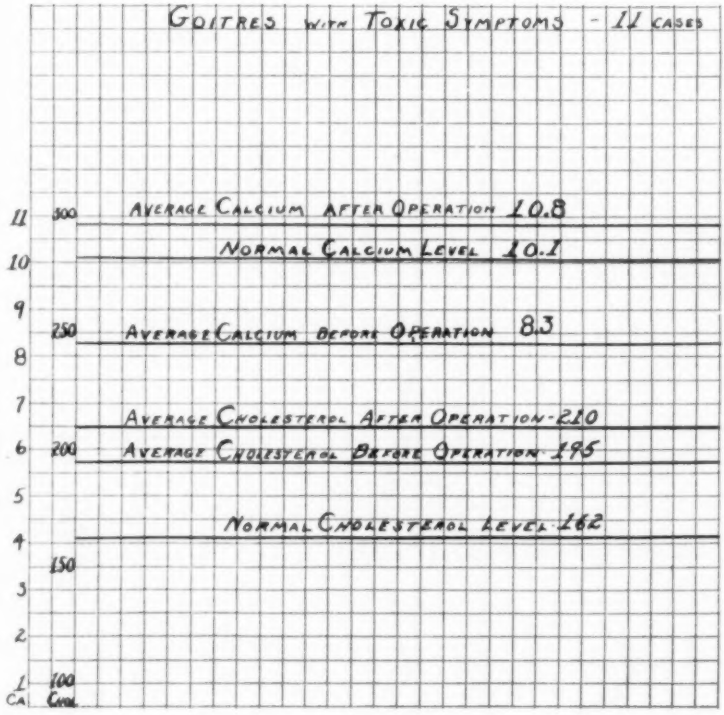


CHART XI.

"Normal" calcium and cholesterol levels were determined by the average of 10 normal individuals. The calcium average was 10.1 mg. per 100 cc. and the cholesterol average was 162 mg. per 100 cc.

In the study of these cases, we found that the calcium was consistently lowered in the untreated cases before operation. The more toxic the case, the more severe the symptoms, and the lower the calcium reading. The average calcium value on 11 untreated cases of toxic thyroid disease was 8.3 mg. per 100 cc. After operation all of the cases showed an increase in calcium in the blood. The average of the 11 cases after operation was 10.8 mg. per 100 cc.

This is thought to be significant of a consistent change in calcium metabolism.

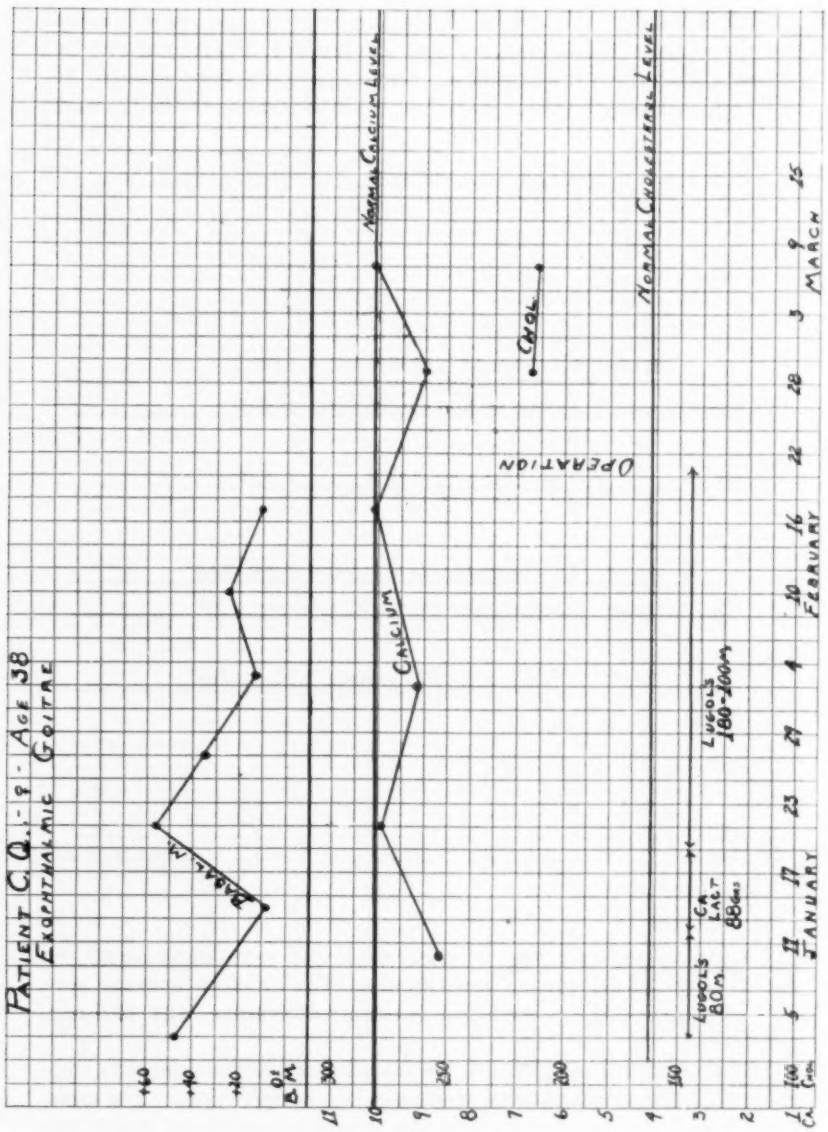


CHART XII.

Cholesterol determination in the 11 cases before operation showed a high level, the average being 195 mg. per 100 cc. After thyroidectomy the cholesterol changes little, but showed a rise, the average being 210 mg. per 100 cc.

In view of the low calcium findings in the severe cases of toxic thyroid disease, with an increase in calcium with the improvement of symptoms, it might be inferred that administration of calcium to these cases would be helpful in allaying symptoms.

Chart XII shows the effect of calcium feeding on a patient with exophthalmic goiter. Admitted with a basal metabolism of +48, the patient was treated by rest in bed with Lugol's solution, 80 minims daily. In one week the basal metabolism fell to +8 with a pro-

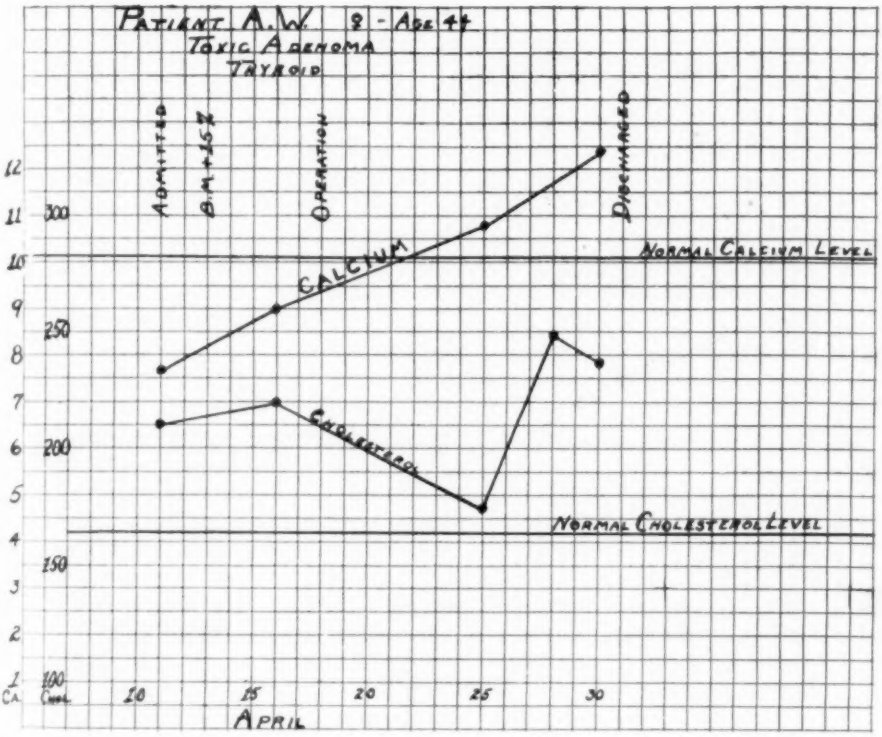


CHART XIII.

portionate alleviation of symptoms. At the end of this time calcium lactate was administered by mouth, 88 gr. daily. As shown in the chart in one week the basal metabolism rose to +58 and symptoms of hyperthyroidism became very much accentuated. The patient had remained in bed during the treatment, but the Lugol's treatment had been discontinued. The blood calcium rose to normal after the administration of calcium lactate by mouth. At the end of the week's experiment the calcium was discontinued and treatment with somewhat larger doses of Lugol's solution instituted.

Under this treatment, the symptoms disappeared quite readily and the basal metabolism rate fell in two weeks to +10. After discontinuance of the calcium treatment, the calcium again fell to a subnormal level but with improvement of symptoms it rose again to normal.

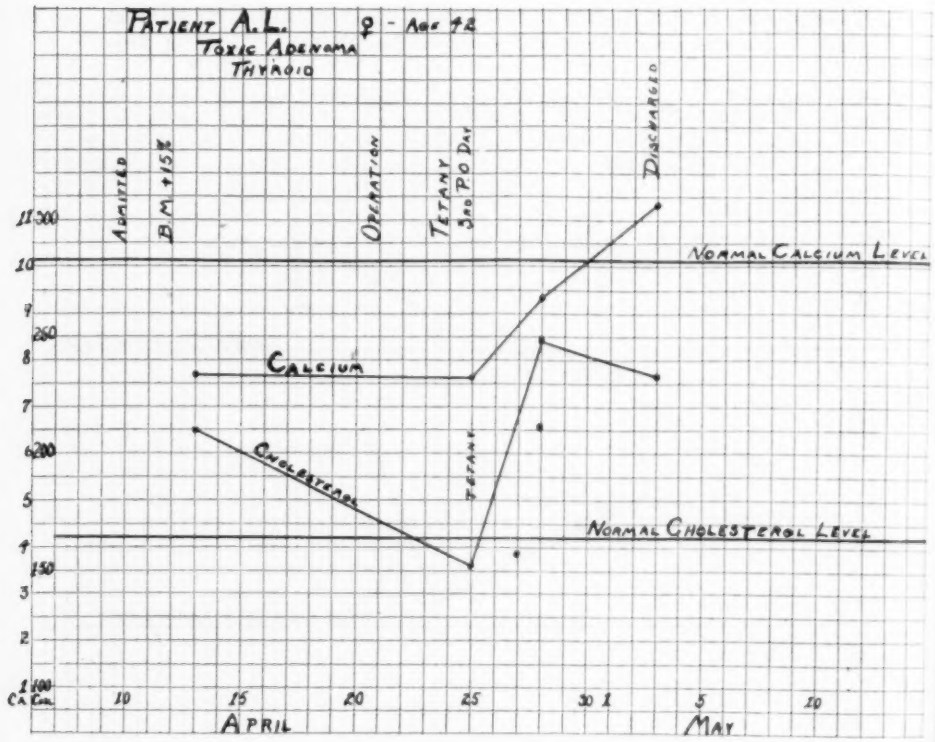


CHART XIV.

It is evident from the experience in this case that although the blood-calcium level is low in exophthalmic goiter, the administration of calcium aggravates the symptoms of the disease. We did not feel justified in repeating this experiment.

Chart XIII, a record of patient A. W., who was afflicted with a toxic adenoma of the thyroid, shows the usual picture of the blood calcium and cholesterol variations. As found in all of these cases the blood calcium was low, 7.6 mg. per 100 cc. Under treatment with rest in bed, the symptoms improved, and the calcium level rose somewhat before operation. After operation with an alleviation of symptoms the calcium rose as indicated to a level well above normal. As would be expected from the experimental work, the

cholesterol findings were high with a low blood calcium. After operation, as the calcium level continued to rise, the cholesterol fell, as expected. However, in both this case and the case of A. L., Chart XIV, there was a secondary rise in the cholesterol which is not explained.

Patient A. L., also having a toxic adenoma of the thyroid, quite similar to the previous case, also had a low blood calcium, 7.7 mg. per 100 cc. on admission. The cholesterol finding was high as in the previous case.

At operation a subtotal resection of the thyroid was done, leaving the posterior portion of both lateral lobes of the thyroid. The parathyroids were not thought to be disturbed either directly or by interference with the blood supply The patient did well after operation until the third day when she suddenly developed typical signs of tetania thyreopriva. There was a period of slight depression, the patient complaining of slight headache and occasional twitchings of the muscles of the hands and feet. There then developed a spastic condition of the hand, the flexor muscles alone being afflicted, so that the contraction assumed the characteristic position of Trousseau, the "accoucheurs hand," with a flexion of the index and middle finger and adduction of the thumb. The condition was bilateral, and of equal severity in both hands. The feet did not seem to be affected, although the feet assumed the tetanic position when pressure was made on the limb (Trousseau's phenomenon). Chovstek's symptom was also present at the time of onset of the attack.

The remarkable finding in this case was the undisturbed calcium level. A blood sample was taken at the onset of the attack before any treatment was instituted and the calcium was found to be 7.6 mg. per 100 cc., practically the same determination as made two weeks before operation. This seemed to indicate that the parathyroids had not been disturbed. The cholesterol determination dropped to a normal level which was indicative also of the fact that the parathyroids had not been disturbed, since in the experimental work the cholesterol almost invariably rose after parathyroidectomy. These findings indicated a good prognosis.

Although it seemed certain that the condition would be temporary and recovery would probably be complete, it did not seem justifiable to delay treatment. Therefore, one dose of 40 units of Collip's parathormone was administered during the attack and an equal dose the following day. The attack subsided gradually and in four hours the symptoms had completely disappeared. For two days thereafter, the patient was somewhat fearful that the symptoms would return, but convalesced rapidly with no further trouble. No further treatment was carried out and the patient was perfectly well when last seen, on November 1, 1928, having had no symptoms since leaving the hospital.

As shown on the chart the blood calcium rose to a point above normal after this attack and there was a secondary rise in the blood cholesterol as in the previous case.

This case seems to give evidence that there is some relationship between the parathyroid glands and the thyroid. When a diseased thyroid was removed, there were signs of parathyroid disturbance, as evidenced by the tetany, in the face of care in the anatomic preservation of the parathyroids and an undisturbed calcium level. As shown in the experimental work of this paper, the blood in a parathyroidectomized animal shows a fall in calcium and a rise in cholesterol. In this instance, tetany occurred without a fall in calcium and with a fall of cholesterol.

**Summary. Action of Cod Liver Oil on Thyroparathyroidectomized Dogs.** 1. An administration of cod-liver oil daily in doses of 20 cc. to 50 cc. over a period of from 14 to 30 days before operation, prolongs the lives of thyroparathyroidectomized dogs. Tetany is delayed and when it appears is diminished in severity. The calcium level falls as in control animals, and reaches a lower level than that of the control animals.

2. Thyroparathyroidectomized dogs may live for long periods of time if they are carried over the critical period of usual fatal tetany by some means such as cod-liver-oil treatment. Fatal tetany may occur at any time in "recovered" dogs.

**Blood Calcium and Cholesterol in Thyroparathyroidectomized Dogs.** 3. There is evidence that there is a relationship between the calcium and cholesterol content of the blood of thyroparathyroidectomized dogs. This perhaps indicates a relationship in the metabolism of calcium and cholesterol.

4. A fall in blood calcium is usually coincident with a rise in blood cholesterol, and *vice versa*.

5. In these experiments the occurrence of a rising cholesterol level in actual tetany was consistent with the occurrence of a decreasing calcium level.

**Observations in Toxic Thyroid Disease.** 6. In toxic thyroid disease, the blood calcium, in this series, was definitely lower than normal. After operation and alleviation of symptoms the calcium level rose consistently to a point above normal.

The blood cholesterol level was raised in these cases before operation, and rose only slightly after operation.

7. Administration of calcium lactate to one case of exophthalmic goiter with a low blood calcium was followed by aggravation of the symptoms of the disease.

8. Tetany occurred in one case of toxic thyroid disease, 3 days after operation. Anatomically the parathyroid glands were thought to be left intact, and the low blood calcium reading during tetany was approximately the same as before operation. The cholesterol level was also low during tetany.

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## THE RELATIONSHIP BETWEEN SEDIMENTATION INDEX AND FIBRIN CONTENT IN RELATIVELY NORMAL INDIVIDUALS.

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**Introduction.** The sedimentation rate of blood cells has interested us for some time.[1,2,3,4] As is well known, one explanation suggested for the rapid sedimentation rate in infections is the increased fibrinogen content. After reviewing previous work on this question we felt that a large series of cases should be studied with a statistical treatment of the data. This method of treating data is fairly new in blood chemistry studies, but we feel that it is to be extremely important in the future. In the course of the investigation, not only the relationship between fibrin content and sedimentation rate,

but also the relationship between fibrin content and age, and between sedimentation rate and age have received attention.

A brief review of previous work on the relationship between fibrin content and sedimentation rate will be given in chronologic order. Pfeiffer[5] suggested such a relationship many years ago. Gram[8] considered the fibrinogen content important in determining the sedimentation rate, through the agglutination of the corpuscles. Fahraeus[9] concluded that an increased fibrinogen content was probably the most important cause for an increased sinking velocity.

Höber and Mond[12] found that fibrinogen decreased the negative charge on the cells, making the suspension less stable, and favoring a faster sedimentation rate. Linzenmeier[13] believed likewise that the fibrinogen content was important in sedimentation. Wöhlisch[14] considered that the speed of sedimentation was affected by the adsorption of fibrinogen on the surface of the red cells. Schindera[16] held the opinion that the sedimentation rate depended upon the fibrinogen content. Holzweissig[19] found that in general a parallel increase of fibrin content occurred with an increased speed of sedimentation. His series included 18 men and 82 women. Bruchsaler[20] found an increased fibrin content accompanying an increased rate of sedimentation in pregnancy. In none of these studies did we find the question of the relationship between fibrin content and sedimentation rate answered to our satisfaction.

A review of the work on the fibrin content of the blood will be given. It will be observed that practically no attention has been directed to the relationship between fibrin content and age. Lewinski[6] found that the fibrin content in healthy men and women ranged from 0.27 to 0.48 per cent. Whipple[7] found that the fibrin content in man varied between 0.3 and 0.6 per cent, with an average of 0.5 per cent. Gram[8] found an average of 0.27 per cent of fibrin in the plasma of 25 men and 0.29 per cent in 25 women. McLester[10] found a range of 250 to 400 mg., with an average of 0.333 per cent for 15 normal individuals, and an average of 0.829 per cent for 20 sepsis patients. The fibrin content seemed fairly constant in health. Gram,[11] in further studies, found that the fibrin content does not vary in the course of the day, nor in relation to meals. He found it increased in tuberculosis, averaging 0.62 per cent in 21 cases.

Foster,[15] in a study of 42 cases, including men from 6 to 63 years of age and women from 16 to 63 years, found an average of 0.332 per cent for men and 0.344 per cent for women. The fibrin content did not parallel the white count. Weltmann[17] found a variation of 0.13 to 0.26 per cent in normal individuals. McLester[18] found a wide variation in fibrin in disease. Bruchsaler[20] found a higher content in women than in men, the normal range being from 64 to 125 mg.

Chandler[21] gives an excellent review of the work on fibrin content

of the blood plasma, discussing the various methods that have been used. In his work he first used the Wu colorimetric method.[22] He states that he found a white precipitate developing in the flasks before the time occurred for matching in the colorimeter. (We had the same difficulty at one time, but learned from Drs. Fahr and Swanson that the phenol reagent must be kept in a cool dark place, and made up freshly each month. Observing these precautions eliminated the difficulty. We experienced another difficulty at one time. The tyrosin standard seemed to lose its original strength. We found a growth, apparently a mold, not only in the tyrosin, but also in the reserve bottle of $\frac{N}{10}$ hydrochloric acid. The whole was discarded, and a new solution of $\frac{N}{10}$ acid made up. No further difficulty was experienced, either in the acid or tyrosin standard.) Chandler's difficulty with the precipitate led him to determine the nitrogen in the fibrin by the Folin microkjeldahl method. In a series of ten normal individuals he found a range of 0.226 to 0.388 per cent, and in 4 cases during menstruation he found a range of 0.125 to 0.304 per cent. He made a fairly extensive study of pregnancy cases, as well.

The question of the relationship between the sedimentation index and age has not been answered by previous work. Consequently, the present piece of work was undertaken to gain information on these three questions: The relationship between fibrin content and sedimentation rate; the relationship between fibrin content and age; the relationship between sedimentation index and age. Our series is great enough to permit statistical treatment of the data, which we believe to be essential in blood chemistry studies. Incidentally, interesting sex differences appeared in the course of the work.

**Results.** This series was carried out on individuals as nearly normal as could be conveniently found at the various ages.[25] The 7 to 17-year group was composed entirely of children attending Lymanhurst School. They were undernourished, but able to attend school regularly. They came from families in rather humble circumstances. They were under observation at Lymanhurst because of previous contact with open cases of tuberculosis.

The 18 to 28-year group consisted of students attending the University of Minnesota. Because of the difference in these first two groups it seemed advisable to base our studies on groups 7 to 17, 18 to 28, 29 to 39 years, and so forth, rather than on decades. Most of the students in the 18 to 28-year group were in very good health. The 29 to 39-year group contained several medical students, several faculty members, and some patients attending the University Dispensary. The patients were derived from various clinics, such as neurology, dermatology and internal medicine. They were all up and about, and engaged in regular work of some sort.

The 40 to 50-year group included some faculty members, some

physicians, and patients, comparable to those in the 29 to 39-year group. The 51 to 61-year group included physicians, some dispensary patients and some individuals of Parkview Sanatorium. These were chronic cases, some suffering from partial paralysis, some from decompensated hearts, some from arthritis, and so forth. They were no longer able to be self-supporting. The 62 to 72-year group included Parkview patients, and dispensary patients, mostly from the ear and heart clinics. The dispensary patients were up and about, of course, as were some of the Parkview patients. Those above 72 were of the same type. While the material used in these studies has not been normal, it may be described as relatively normal, since most of the individuals were up and about, and working, and were free from acute infection.

The blood was drawn by venepuncture, usually about two hours after the last meal. The sedimentation rate was determined by the Cutler graphic method,[23] using 0.5 cc. of potassium oxalate (4.4 per cent) instead of citrate. Readings were taken at 15-, 30-, 45- and 60-minute intervals, except in one additional group, in which readings were taken at frequent intervals over a 19-hour period. The fibrin was determined in duplicate on plasma from the same sample as used for the sedimentation rate. The Wu colorimetric method[22] was used, with slight modification, observing the precautions mentioned in the introduction.

1. **Entire Group of Each Sex.** The series included 200 women and 213 men, ranging in age from 7 to 94 years. The average sedimentation index (one hour reading) for women was $9.54 \pm 0.25$ mm.; the range was from 1 to 28 mm. The average index for men was $8.14 \pm 0.34$ mm., with a range of 1 to 31 mm. The difference between the sexes is $1.39 \pm 0.42$ mm. This is 3.3 times as large as its probable error. Similar differentiation exists in tuberculosis patients.[24] Our results substantiate in a quantitative way the findings of earlier investigators.

The average fibrin content for women was $0.3045 \pm 0.0027$ gm. per 100 cc. of plasma. The range was from 0.20 to 0.55 gm. The average fibrin content for men was $0.3253 \pm 0.0039$ gm., the range being from 0.20 to 0.80 gm. The difference between the sexes is $0.0208 \pm 0.0047$ gm. Being 4.4 times as large as its probable error, it is significant. Similar differentiation was found in tuberculous patients.[24] We differ from other investigators in finding the average fibrin content lower in women than in men.

The usual statistical methods have been employed. For advice in connection with the use of these methods we are greatly indebted to Prof. J. Arthur Harris. A study of the relationship between fibrin content and sedimentation index gave a correlation coefficient, $r_{FS}$, of $0.533 \pm 0.034$ for the women. (F = grams of fibrin per 100 cc. of plasma and S = sedimentation index in millimeters.)

The correlation is significant, since it is 15.7 times as large as its probable error.

The linear regression equation, calculated from the means, standard deviations, and correlation coefficient is F = 0.2492+ 0.0058S, where, as above, F = grams of fibrin per 100 cc. of plasma and S = the sedimentation index in millimeters. The empirical mean fibrin contents as ordinates are plotted against the indices in Chart I.

The correlation coefficient, $r_{FS,}$ for the men was 0.749±0.020. This is 37.4 times as large as its probable error. The linear regression equation is F = 0.2547+0.0087 S. The empirical mean fibrin values as ordinates are plotted against the indices in Chart I.

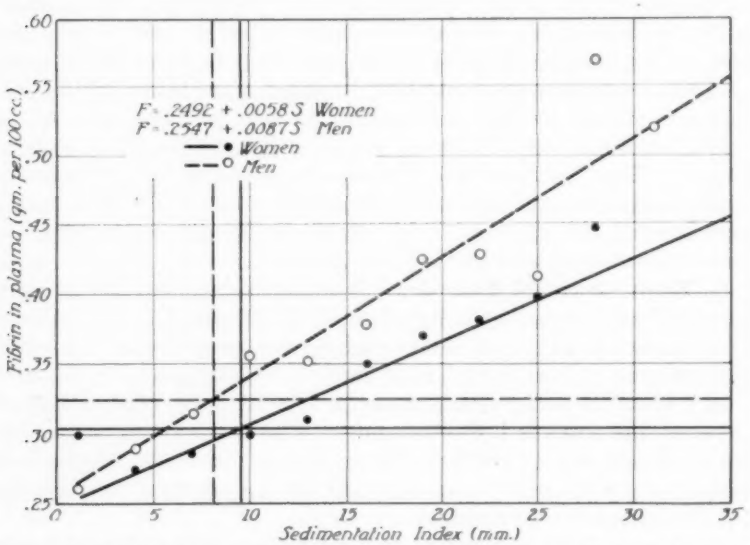


CHART I.—Relatively normal individuals, relationship between fibrin content and sedimentation index.

The difference between the correlation coefficients for the two sexes is 0.216±0.039. We are unable to account for the significantly greater correlation in men.

2. **Investigation of Women of Different Ages.** The foregoing results were found on the entire group of women. The group will now be divided into 6 subgroups, according to age. The subgroups will include women from 7 to 17, 18 to 28, 29 to 39, 40 to 50, 51 to 61 and 62 to 72 years of age. The results for each subgroup are presented in Table I.

It will be observed in Table I that the index tends to increase with age. The fibrin first decreases, then increases. The correlation coefficient is significant in every group.

TABLE I.—RELATIVELY NORMAL WOMEN. AVERAGE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT OF EACH SUBGROUP AND THE ENTIRE GROUP.

| No. | Age. | Index, mm. | | Fibrin, gm. per 100 cc. of plasma. | | Corr. coeff., $r_{FS} \pm$P.E. | $\frac{r}{\text{P.E.}_r}$ |
|---|---|---|---|---|---|---|---|
| | | Average. | Range. | Average. | Range. | | |
| 24 | 7–17 | 6.50 | 4–16 | 0.3021 | 0.25–0.35 | 0.374 ±0.118 | 3.1 |
| 75 | 18–28 | 7.76 | 1–16 | 0.2840 | 0.20–0.45 | 0.322 ±0.070 | 4.6 |
| 27 | 29–39 | 7.56 | 1–19 | 0.2815 | 0.20–0.40 | 0.320 ±0.116 | 2.7 |
| 25 | 40–50 | 12.40 | 4–22 | 0.3240 | 0.25–0.55 | 0.577 ±0.090 | 6.4 |
| 25 | 51–61 | 13.72 | 4–28 | 0.3420 | 0.25–0.50 | 0.644 ±0.079 | 8.1 |
| 18 | 62–72 | 11.83 | 4–22 | 0.3278 | 0.25–0.45 | 0.373 ±0.137 | 2.7 |
| 200 | 7–94 | 9.53 | 1–28 | 0.3045 | 0.20–0.55 | 0.533 ±0.034 | 15.7 |

The deviations of the index, fibrin content and correlation coefficient for the subgroups, classified according to age, from the comparable constants for the group as a whole are shown in Table II. These differences are taken (constant for subgroup) less (constant for entire group), in order to give signs which will show whether the constants for the subgroups are larger or smaller than those for the entire group.

TABLE II.—DEVIATIONS OF THE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT FOR THE SUBGROUPS, FROM THE COMPARABLE CONSTANTS FOR THE GROUP AS A WHOLE. THE ENTIRE GROUP CONSTANTS ARE THE SUBTRAHENDS.

| Age. | Deviation of index. | Deviation of fibrin content. | Deviation of correl. coeff. |
|---|---|---|---|
| 7–17 | −3.03 | −0.0024 | −0.159 |
| 18–28 | −1.77 | −0.0205 | −0.211 |
| 29–39 | −1.97 | −0.0230 | −0.213 |
| 40–50 | +2.87 | +0.0195 | +0.044 |
| 51–61 | +4.19 | +0.0375 | +0.111 |
| 62–72 | +2.30 | +0.0233 | −0.160 |

The first three subgroups have a smaller index, the last three a larger index than the entire group. The fibrin contents are lower in the first three subgroups and higher in the last three, than in the entire group. The correlation coefficient is smaller in all the subgroups except the 40 to 50- and 51 to 61-year groups, than in the group as a whole.

An additional group of 56 women, mostly between 18 and 30 years of age, was studied to determine if the one-hour reading gave as reliable a picture of the relationship between the fibrin content and the sedimentation rate as readings at other intervals. Table III presents for each time interval the average index, the correlation

coefficient and the deviation of the latter from the coefficient for the 1-hour reading. These differences are taken (coefficient for given interval) less (coefficient for 1-hour reading), in order to give signs which will show whether the coefficients for the various time intervals are larger or smaller than that for the 1-hour reading.

TABLE III.—FIFTY-SIX NORMAL WOMEN. THE AMOUNT OF SEDIMENTATION, THE CORRELATION COEFFICIENT, $r_{FS,}$ AND THE DEVIATION OF THIS COEFFICIENT FROM THE 1-HOUR COEFFICIENT. (THE AVERAGE FIBRIN CONTENT FOR THIS GROUP WAS 0.2732 ± 0.0044 GM. PER 100 CC. OF PLASMA.)

| Time. | Sed., mm. | Coeff. of corr., $r_{FS} \pm$ P.E. | $\frac{r}{\text{P.E.}_r}$ | Deviation of correl. coeff. | $\frac{\text{Diff.}}{\text{P.E. diff.}}$ |
|---|---|---|---|---|---|
| 15 min. | 1.32 | 0.462 ± 0.071 | 6.5 | −0.115 ± 0.092 | 1.20 |
| 30 " | 4.27 | 0.562 ± 0.062 | 9.0 | −0.015 ± 0.086 | 0.20 |
| 45 " | 7.00 | 0.623 ± 0.055 | 11.3 | +0.046 ± 0.082 | 0.50 |
| 1 hr. | 9.36 | 0.577 ± 0.060 | 9.6 | | |
| 1½ hrs. | 12.14 | 0.573 ± 0.060 | 9.5 | −0.004 ± 0.084 | 0.05 |
| 2 " | 14.12 | 0.589 ± 0.059 | 9.9 | +0.012 ± 0.084 | 0.10 |
| 4 " | 18.03 | 0.582 ± 0.059 | 9.8 | +0.005 ± 0.084 | 0.06 |
| 6 " | 19.43 | 0.530 ± 0.065 | 8.2 | −0.045 ± 0.088 | 0.50 |
| 8 " | 20.08 | 0.521 ± 0.065 | 8.0 | −0.056 ± 0.088 | 0.60 |
| 10 " | 20.55 | 0.510 ± 0.066 | 7.7 | −0.067 ± 0.089 | 0.70 |
| 19 " | 21.36 | 0.462 ± 0.071 | 6.5 | −0.115 ± 0.092 | 1.20 |

The correlation coefficient is significantly greater than its probable error at every time interval studied. Thus the readings at any time interval, corrected to a standard time interval, may be used to determine the relationship between fibrin content and sedimentation rate. The deviations of the coefficient at the given time interval from the 1-hour coefficient are insignificant.

A study of the relationship between sedimentation index and age gave a coefficient, $r_{AS,}$ of 0.486 ± 0.036 for the women. (A = age in years and S = sedimentation index in millimeters.) The coefficient is 13.5 times as large as its probable error. The linear regression equation is S = 4.52+0.14 A, where, as above S = sedimentation index in millimeters, and A = age in years. The empirical mean indices as ordinates are plotted against the age in Chart 2.

The correlation coefficient, $r_{AF,}$ between fibrin content and age was 0.355 ± 0.042 for the women. The coefficient is 8.4 times as large as its probable error. The linear regression equation is F = 0.2646+0.0011 A, where F = grams of fibrin per 100 cc. of plasma and A = age in years. The empirical mean fibrin contents as ordinates are plotted against the age in Chart 3.

3. **Investigation of Men of Different Ages.** The results for the group of men as a whole have been given. The subgroups, according

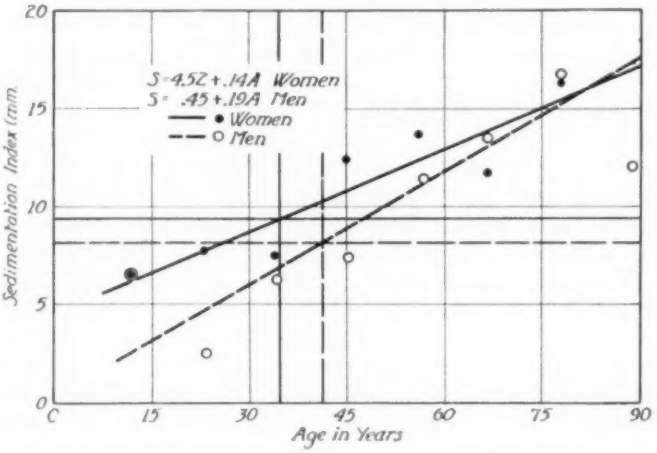


CHART II.—Relationship between sedimentation index and age.

to age, include men from 7 to 17, 18 to 28, 29 to 39, 40 to 50, 51 to 61, 62 to 72 and 73 to 83 years of age. The results for each subgroup are presented in Table IV.

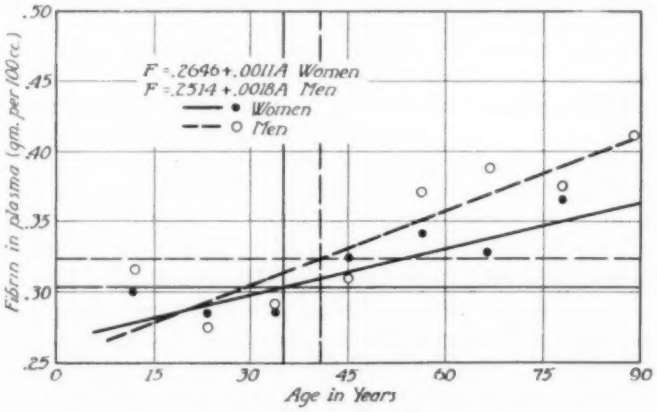


CHART III.—Relationship between fibrin content and age.

As seen in Table IV, the index increases with age, except in the 18- to 28-year group. The fibrin content first decreases, then increases. The correlation coefficient is significant in every group with the exception of the 18 to 28-year group.

TABLE IV.—RELATIVELY NORMAL MEN. AVERAGE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT OF EACH SUBGROUP AND THE ENTIRE GROUP.

| No. | Age. | Index, mm. | | Fibrin, gm. per 100 cc. of plasma. | | Corr. coeff., $r_{FS} \pm P.E.$ | $\frac{r}{P.E._r}$ |
|---|---|---|---|---|---|---|---|
| | | Average. | Range. | Average. | Range. | | |
| 30 | 7–17 | 6.60 | 1–16 | 0.3183 | 0.20–0.40 | $0.497 \pm 0.093$ | 5.3 |
| 53 | 18–28 | 2.53 | 1– 7 | 0.2707 | 0.20–0.40 | $0.167 \pm 0.090$ | 1.8 |
| 26 | 29–39 | 6.08 | 1–28 | 0.2904 | 0.20–0.50 | $0.769 \pm 0.054$ | 14.2 |
| 27 | 40–50 | 7.33 | 1–28 | 0.3093 | 0.25–0.55 | $0.757 \pm 0.055$ | 13.7 |
| 26 | 51–61 | 11.50 | 4–25 | 0.3731 | 0.25–0.55 | $0.747 \pm 0.058$ | 12.8 |
| 31 | 62–72 | 13.68 | 1–31 | 0.3903 | 0.20–0.80 | $0.746 \pm 0.054$ | 13.8 |
| 17 | 73–83 | 16.88 | 4–31 | 0.3794 | 0.30–0.50 | $0.512 \pm 0.120$ | 4.3 |
| 213 | 7–94 | 8.14 | 1–31 | 0.3253 | 0.20–0.80 | $0.749 \pm 0.020$ | 37.4 |

The deviations of the index, fibrin content and correlation coefficient for the subgroups, classified according to age, from the comparable constants for the group as a whole are as shown in Table V. These differences are taken (constant for subgroup) less (constant for entire group), in order to give signs which will show whether the constants for the subgroup are larger or smaller than those for the entire group.

TABLE V.—DEVIATIONS OF THE INDEX, FIBRIN CONTENT AND CORRELATION COEFFICIENT FOR THE SUBGROUPS, FROM THE COMPARABLE CONSTANTS FOR THE GROUP AS A WHOLE.

| Age. | Deviation of index. | Deviation of fibrin content. | Deviation of correl. coeff. |
|---|---|---|---|
| 7–17 | −1.54 | −0.0070 | −0.252 |
| 18–28 | −5.61 | −0.0546 | −0.582 |
| 29–39 | −2.06 | −0.0349 | +0.020 |
| 40–50 | −0.81 | −0.0168 | +0.008 |
| 51–61 | +3.36 | +0.0478 | −0.002 |
| 62–72 | +5.54 | +0.0650 | −0.003 |
| 73–83 | +8.74 | +0.0541 | −0.237 |

The first four subgroups have a smaller index and a lower fibrin content than the group as a whole. The last three subgroups have a larger index and a higher fibrin content than the group as a whole. The correlation is smaller in all the subgroups except the 29 to 39- and 40 to 50-year groups, than in the group as a whole.

A study of the relationship between sedimentation index and age gave a coefficient, $r_{AS}$, of $0.554 \pm 0.032$ for the men. (S = sedimentation index in millimeters and A = age in years.) The coefficient is 17.3 times as large as its probable error. The linear regression equation is $S = 0.45 + 0.19\ A$. The empirical mean sedimentation indices as ordinates are plotted against the age in Chart 2.

The correlation coefficient, $r_{AF,}$ between fibrin content and age was $0.460 \pm 0.036$ for the men. This is 12.8 times as large as its probable error. The linear regression equation is $F = 0.2514 \pm 0.0018$ A, where F = grams of fibrin per 100 cc. of plasma and A = age in years. The empirical mean fibrin contents as ordinates plotted against the age in Chart 3.

We hope that future work will include reinvestigation of the origin of fibrinogen, the mechanism of its increase in infections and the cause for the more rapid sedimentation of blood cells in various diseases. Although we have found a significant correlation between fibrin content and sedimentation rate in all cases but one, we do not consider the relationship a causal one. The chief reason for this point of view lies in the fact that women have a statistically significantly faster sedimentation rate than men, with a lower fibrin content.

**Summary.** 1. The sedimentation index (Cutler graphic method) in a series of 200 relatively normal women averaged $9.54 \pm 0.25$ mm.; in 213 relatively normal men it averaged $8.14 \pm 0.34$ mm. The difference between the two sexes is $1.39 \pm 0.42$, which is statistically significant, as in tuberculous patients.[24]

2. The fibrin content (Wu colorimetric method) for the women averaged $0.3045 \pm 0.0027$ gm. per 100 cc. of plasma. The average for the men was $0.3253 \pm 0.0039$ gm. The difference between the two sexes is $0.0208 \pm 0.0047$ gm., which is statistically significant. Similar sex differentiation exists in tuberculous men and women.[24]

3. The correlation coefficient, $r_{FS,}$ between fibrin content and sedimentation index is $0.533 \pm 0.034$ for the women and $0.749 \pm 0.020$ for the men. Both show a significant relationship between fibrin and sedimentation rate. We have no explanation for the significantly greater correlation in the men.

4. The average index increased from $6.50 \pm 0.44$ mm. in the 7 to 17-year group to $11.83 \pm 0.86$ mm. in the 62 to 72-year group of relatively normal women. The difference between the highest and lowest age groups is $5.33 \pm 0.97$ mm. The difference is statistically significant. The coefficient of correlation ($r_{AS}$) between sedimentation index and age is $0.485 \pm 0.036$.

In the men the average index increased from $6.60 \pm 0.40$ mm. in the 7 to 17-year group to $13.68 \pm 1.0$ mm. in the 62 to 72-year group. The difference between these age groups is $7.08 \pm 1.1$ mm. The coefficient of correlation ($r_{AS}$) between sedimentation index and age is $0.553 \pm 0.032$. Both sexes show a significant relationship between sedimentation index and age.

5. The average fibrin content increased from $0.3021 \pm 0.0037$ gm. in the 7 to 17-year group to $0.3278 \pm 0.0085$ gm. in the 62 to 72-year group of women. The difference between these groups is $0.0257 \pm$

0.0093 gm. The coefficient of correlation, $r_{AF,}$ between fibrin and age in women is $0.355 \pm 0.042$.

In men the average fibrin content increased from $0.3183 \pm 0.0063$ gm. in the 7 to 17-year group to $0.3903 \pm 0.0145$ gm. in the 62 to 72-year group. The difference between these groups is $0.072 \pm 0.016$ gm. The coefficient of correlation, $r_{AF,}$ is $0.459 \pm 0.035$. Both sexes show a significant relationship between fibrin content and age.

6. In both sexes a significant correlation between fibrin content and sedimentation index exists, not only in the groups as a whole, but also in the subgroups, with the exception of the 18 to 28-year group of men.

7. In an additional group of 56 women significant correlation was found between the fibrin content and the amount of sedimentation at 15, 30 and 45 minutes, 1, 1½, 2, 4, 6, 8, 10 and 19 hours. There was excellent agreement between the coefficients so found.

**Conclusions.** From the above results we draw the following conclusions:

1. The sedimentation rate of red cells is faster in women than it is in men.

2. The fibrin content is lower in women than it is in men.

3. As the fibrin content increases, the sedimentation rate becomes more rapid. The relationship is more constant in men than it is in women. Although this relationship between fibrin content and sedimentation rate is evident in both sexes, we are not convinced that it is a causal one. Our chief reason for this is the fact that women have a lower fibrin content, but a faster sedimentation rate than men. The question must receive further study.

4. The sedimentation rate increases with age in both men and women.

5. The fibrin content increases with age in both men and women.

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## INCREASE IN BLOOD SUGAR FOLLOWING THE INGESTION OF GLYCEROL.

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Voegtlin, Dunn and Thompson have reported observations indicating that intraperitoneal injections of glycerol can prevent and relieve hypoglycemic shock in albino rats.[1] In this animal, the curative effect, which requires only about ten minutes, approximates the effect produced by the injection of a similar amount of glucose. According to these authors, glycerol will also relieve the hypoglycemic symptoms following the injection of insulin in rabbits, although in this animal larger doses are required—8 to 12 gm. per kilo of body weight.

These authors suggest that the antagonistic action of glycerol on insulin is due to a conversion of glycerol into glucose. In order to test this possibility, they have determined the effect of glycerol on the blood sugar concentration of fasted rabbits.[2] In these experiments they found that glycerol given to fasted rabbits per os or intraperitoneally produces a hyperglycemia of considerable extent and duration. They have concluded that this indicates a conversion of glycerol into sugar.

TABLE I.—INFLUENCE OF 100 GM. GLYCEROL ON THE BLOOD SUGAR IN CASES OF DIABETES.

| Case. | Sex. | Age. | Blood sugar, Mg. per cent. Fasting. | 1 hr. | 2 hr. | 3 hr. | Urine, sugar. Fasting. | 1 hr. | 2 hr. | 3 hr. |
|---|---|---|---|---|---|---|---|---|---|---|
| 4, N. N. | M. | 57 | 90 | .. | 150 | .. | Neg. | .... | Neg. | |
| 9, M. K. | F. | 57 | 190 | .. | 230 | 250 | Neg. | .... | 2% | 2% |
| 10, A. T. | M. | 66 | 160 | .. | 190 | 190 | Neg. | .... | Neg. | Neg. |
| 11, P. C. | F. | 58 | 125 | .. | 130 | 140 | Neg. | .... | Neg. | Neg. |
| 12, P. P. | F. | 45 | 220 | .. | 220 | 200 | Neg. | .... | Neg. | Neg. |
| 13, E. R. | F. | 39 | 170 | .. | 230 | 270 | Neg. | .... | Neg. | Neg. |
| 15, R. T. | M. | 53 | 260 | .. | 350 | 330 | 95 cc.–1% | .... | 100 cc.–2.2% | 75 cc.–1.4% |
| 16, E. T. | F. | 52 | 210 | .. | 240 | .. | Neg. | .... | Neg. | |
| 17, M. S. | F. | 50 | 170 | .. | 195 | 175 | Neg. | .... | Neg. | Neg. |
| 18, E. R. | F. | 57 | 115 | 160 | .. | .. | Neg. | Neg. | | |
| 20, B. C. | F. | 64 | 250 | .. | 360 | 300 | 5 cc.–0.5% | .... | 100 cc.–0.5% | 100 cc.–0.5% |
| 22, I. | F. | 47 | 85 | .. | 130 | 130 | Neg. | .... | Neg. | Neg. |
| 23, H. G. | F. | 55 | 220 | .. | 210 | .. | 15 cc.–0.5% | .... | 400 cc.–2% | |
| 24, B. S. | F. | 46 | 105 | .. | 160 | .. | Neg. | .... | Neg. | |
| 27, D. B. | F. | 40 | 200 | .. | 200 | 190 | Neg. | .... | Neg. | Neg. |
| 28, A. R. | F. | 52 | 140 | .. | 180 | 160 | Neg. | .... | Neg. | Neg. |
| 29, S. | M. | 50 | 100 | .. | 145 | 125 | Neg. | .... | Neg. | Neg. |
| 30, C. | F. | 47 | 230 | .. | 230 | 300 | 50 cc.–0.5% | .... | 150 cc.–tr. | 200 cc.–Neg. |
| 31, A. O'C. | F. | 58 | 190 | .. | 170 | .. | 25 cc.–1% | .... | 50 cc.–tr. | |
| 32, S. | M. | 38 | 95 | .. | 130 | | | | | |
| 33, J. L. | F. | 55 | 110 | .. | 180 | .. | Neg. | .... | 0.5% | |
| 35, D. K. | F. | 65 | 160 | .. | 210 | 230 | Neg. | .... | Neg. | Neg. |
| 36, C. M. | F. | 58 | 160 | .. | 300 | 200 | Neg. | .... | Neg. | 1 plus |
| 37, J. C. | M. | 54 | 200 | .. | 180 | 200 | Neg. | .... | Neg. | Neg. |
| 38, L. C. | F. | 60 | 190 | .. | 220 | 200 | Neg. | .... | Neg. | Neg. |
| 39, F. S. | F. | 62 | 85 | .. | 170 | 84 | Neg. | .... | Neg. | Neg. |
| 41, M. C. | F. | 65 | 170 | .. | 180 | .. | Faint trace | .... | Faint trace | |
| 42, M. H. | M. | 29 | 290 | 310 | .. | .. | 75 cc.–5% | 55 cc.–7.1% | | |
| 43, H. S. | F. | 55 | 134 | 166 | .. | .. | Neg. | Neg. | | |
| 44, P. G. | M. | 62 | 110 | .. | 160 | .. | Neg. | .... | Neg. | |
| 46, A. B. | F. | 54 | 140 | .. | 160 | .. | Trace | .... | Neg. | |
| 47, J. R. | M. | 63 | 180 | .. | 180 | 180 | Neg. | .... | Neg. | Neg. |
| 49, E. M'C. | M. | 67 | 125 | .. | 165 | 170 | Trace | .... | Trace | Neg. |
| 50, H. R. | M. | 63 | 105 | .. | 140 | 140 | Neg. | .... | Neg. | Neg. |
| 55, D. K. | M. | 63 | 290 | .. | 308 | 266 | 1 plus | .... | 1 plus | 1 plus |
| 56, J. G. | F. | 53 | 130 | .. | 121 | 160 | Neg. | .... | Neg. | Neg. |
| 57, V. C. | F. | 35 | 180 | .. | 225 | 204 | Neg. | .... | 1 plus | 1 plus |
| 58, F. | F. | 58 | 155 | .. | 230 | 190 | Neg. | .... | 1 plus | 1 plus |
| 59, M. S. | M. | 45 | 110 | .. | 115 | .. | Neg. | .... | Neg. | Neg. |
| 60, D. K. | F. | 50 | 110 | .. | 125 | 125 | Neg. | .... | Neg. | Neg. |

TABLE II.—INFLUENCE OF 100 GM. GLYCEROL ON THE BLOOD SUGAR IN CASES OF DOUBTFUL DIABETES.

| Case. | Sex. | Age. | Blood sugar, Mg. per cent. Fasting. | 1 hr. | 2 hr. | 3 hr. | Urine, sugar. Fasting. | 1 hr. | 2 hr. | 3 hr. |
|---|---|---|---|---|---|---|---|---|---|---|
| 14, S. G. | F. | 42 | 120 | .. | 115 | 110 | Neg. | .. | Neg. | Neg. |
| 19, S. D. | F. | 50 | 100 | 116 | .. | .. | Neg. | Neg. | | |
| 21, M. C. | M. | 44 | 105 | 130 | .. | .. | Neg. | Neg. | | |
| 25, A. S. | F. | 48 | 75 | .. | 76 | .. | Neg. | .. | Neg. | |
| 34, S. A. | F. | 62 | 92 | .. | 110 | .. | Neg. | .. | Neg. | |
| 40, E. N. | F. | 58 | 135 | .. | 135 | .. | Trace | .. | Faint trace | |
| 53, M. P. | F. | 32 | 95 | .. | 85 | .. | Neg. | | | |

TABLE III.—INFLUENCE OF 100 GM. GLYCEROL ON THE BLOOD SUGAR IN NONDIABETICS.

| Case. | Sex. | Age. | Blood sugar, Mg. per cent. Fasting. | 1 hr. | 2 hr. | 3 hr. | Urine, sugar. Fasting. | 1 hr. | 2 hr. | 3 hr. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Neuralgia | F. | 41 | 100 | 112 | .. | .. | Neg. | Neg. | .. | Neg. |
| 2. Arthritis | M. | 43 | 75 | .. | 75 | 60 | Neg. | .. | Neg. | Neg. |
| 3. Arthritis | M. | 43 | 95 | .. | 95 | 75 | Neg. | .. | Neg. | Neg. |
| 5. Nephritis | F. | 17 | 114 | .. | 95 | 90 | Neg. | .. | Neg. | |
| 6. Arthritis | F. | 50 | 72 | 104 | .. | .. | Neg. | Neg. | | |
| 7. Arthritis | F. | 47 | 140 | 175 | .. | .. | Neg. | Neg. | | |
| 8. Hypertension | F. | 48 | 85 | 95 | .. | .. | Neg. | Neg. | | |
| 26. Hypertension | F. | 53 | 70 | .. | 65 | .. | Neg. | .. | Neg. | |
| 45. Sciatica | M. | 56 | 100 | 95 | .. | .. | Neg. | Neg. | | |
| 48. Hypertension | F. | 65 | 120 | .. | 90 | .. | Neg. | .. | Neg. | |
| 51. Hypertension | F. | 48 | 88 | .. | 76 | .. | Neg. | .. | Neg. | |
| 52. Post operative gall bladder | F. | 59 | 100 | .. | 160 | .. | Neg. | .. | Neg. | |
| 54. Exophthalmic goiter | M. | 33 | 95 | .. | 120 | .. | Neg. | .. | Neg. | |

TABLE IV.—SHOWING THAT NONFERMENTABLE SUGAR IS NOT INFLUENCED BY THE RISE IN BLOOD SUGAR CAUSED BY THE INGESTION OF GLYCEROL AND THAT THIS INCREASE IS FERMENTED BY YEAST.

| Case. | Blood sugar, Mg. per cent. Fasting. | 2 hr. | 3 hr. | Nonfermentable "rest reduction," Mg. per cent. Fasting. | 2 hr. | 3 hr. |
|---|---|---|---|---|---|---|
| 4. Diabetes | 90 | 150 | ... | 17 | 20 | |
| 16. Diabetes | 210 | 240 | ... | .. | 17 | |
| 17. Diabetes | 170 | 175 | 175 | 33 | 40 | 36 |
| 32. Diabetes | 95 | 130 | ... | 20 | 24 | |
| 46. Diabetes | 140 | 160 | ... | 11 | 10 | |
| 51. Hypertension | 88 | 76 | ... | 14 | 20 | |
| 52. Postoperative gall bladder | 100 | 160 | ... | 14 | 22 | |
| 53. Diabetes (?) | 95 | 85 | ... | 10 | 8 | |
| 54. Exophthalmic goiter | 95 | 120 | ... | 10 | 14 | |

In our observations we have determined the effect of glycerol on the blood sugar of 60 patients. Of these, 40 were definitely diabetic, 7 were doubtful diabetics, 4 were cases of hypertension, 4 of arthritis, 1 of nephritis (mild, with normal blood chemistry), 1 of exopthalmic goiter, 2 of neuralgia, and 1 had gall stones removed. We classify as doubtful diabetics those cases who while under our observation had no sugar in the urine, had a normal fasting blood sugar, some

giving a negative blood-sugar curve after the ingestion of 100 gm. glucose, but with a history of glycosuria previous to our observation.

**Method of Procedure.** The patient was given on an empty stomach at least ten hours after last meal, 100 gm. glycerol in 250 to 300 cc. of water. At the beginning the glycerol was divided into two doses and given at a fifteen-minute interval, but later the whole amount was given in one dose. Blood was withdrawn immediately before and then again in two and three hours after the administration of glycerol. In some cases blood was withdrawn before and then only once, one or two hours after the glycerol. In each case the urine passed by the patient just before the withdrawal of each sample of blood, was tested for sugar.

Fermentation by yeast is considered the most accurate method for the determination of sugar, and modern investigators are increasingly using the fermentation process for the determination of blood sugar. The term "sugar" as commonly applied to the blood, includes all the substances determined by the reduction method. These include glucose, unknown sugars and some nitrogenous products in the tungstic acid blood filtrates. Yeast fermentation removes all the glucose and other unknown sugars but leaves the nitrogenous products. These are designated as nonfermentable sugars (rest reduction). This nonfermentable sugar is, according to Folin and Svedberg, independent of the original sugar level of the blood and amounts to about 20 mg. per cent when Folin-Wu reagent is used. According to these authors, the yeast works just as expeditiously in tungstic acid filtrate as in pure sugar solution.[3] In 9 of our series of cases, the tungstic acid blood filtrate was fermented with yeast in order to determine whether the increase in reducing substances caused by the ingestion of glycerol, is removable by fermentation. If this increase is removable by fermentation, then it must be due to glucose and other unknown sugars, and not to the nitrogenous products in the filtrate. There are no known practical chemical means of differentiating glucose from other unknown sugars in the blood, and from the chemical point of view, such substances as glyceric aldehyde, which may be produced from glycerol within the body, cannot be excluded. The figures given in Table IV are those of the nonfermentable fraction of reducing substances (rest reduction) after the others have been removed by yeast. These are also the uncorrected figures, that is, without subtracting the "blank" which is gotten by suspending yeast in water, and is equivalent to from 3 to 5 mg. per cent.

**Clinical Reaction.** In general, there was little if any reaction following the ingestion of glycerol. In no instance were there any gastrointestinal disturbances reported such as vomiting or diarrhea. Only 5 patients complained of any discomfort, which was usually a throbbing headache or dizziness and in one case was associated with marked erythema of the face. The erythema in the last case was

followed by some scaling of the skin. The headache in some of the cases might well have been due to lack of food. Of the 5 patients who had any unpleasant reaction only one, Case VI, gave a rise in the reducing substances of the blood. It is reasonable to assume that the discomfort of the patient had no effect on this rise.

**Discussion.** In the laboratory, glycerol may be converted into hexose. It is believed that in this process, dioxyacetone and glyceric aldehyde are formed and that two molecules of either of these may be polymerized to form a hexose molecule. When this process occurs in the animal body, the hexose formed is glucose.[4] Voegtlin and his collaborators have shown that the rise in blood sugar following the administration of glycerol to rabbits, is not due to a concentration of the blood. On the other hand, they could not exclude the possibility that the increase in blood sugar might be due to glyceric aldehyde produced from glycerol within the body.

From an analysis of our case reports, it will be seen that the very marked rises in blood sugar occurred in the more progressive case of diabetes. Twenty-seven of the 40 cases of diabetes (67.5 per cent) show an increase of 20 or more mg., while only one of seven doubtful cases shows an increase of 25 mg. Four cases of hypertension gave no increase whatsoever. Of the 4 cases of arthritis, 2 show no rise, 1 had a fasting blood sugar of 140 and should, therefore, be considered as a potential diabetic. Only Case VI shows a rise of 32 mg. one hour after the glycerol. One case of sciatica gave no increase, while a case of neuralgia gave an increase of only 12 mg. Case 52 (recent gall bladder operation) does indeed show an increase of 60 mg. two hours after the glycerol. The well known association of diabetes with infections of the biliary tract suggests the possibility that this case is a potential diabetic. One case of nephritis gave no increase and the case of exophthalmic goiter gave an increase of 25 mg.

If the rise in blood sugar is due to glyceric aldehyde, one would find it difficult to explain the difference in behavior between the diabetic and the nondiabetic person. The hyperglycemia curve in a diabetic after the ingestion of glycerol resembles, in its extent as well as in its duration, the curve obtained after the ingestion of glucose. In Case 9, the fasting blood sugar was 190 mg. and the urine was negative. Two hours after the ingestion of glycerol the blood sugar was 230 mg. and the urine contained 2 per cent of sugar. Three hours after the blood sugar was 250 mg. and the urine showed 2 per cent of sugar. Cases 20, 23, 33, 36 and 42 show that part of glycerol is excreted as sugar in the urine.

These observations, we believe, favor the conclusion of Voegtlin and others, namely, that the increase in blood sugar following the ingestion of glycerol, is due to the extra presence of glucose.

**Summary.** Glycerol given to a human being on an empty stomach, will produce a hyperglycemia. The extent of the hyper-

glycemia is in direct ratio to the disturbance of carbohydrate metabolism of the particular individual. In the more progressive cases of diabetes, the glycerol may produce a glycosuria as well as a hyperglycemia. These facts warrant the conclusion that in the human body, glycerol is converted into glucose.

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## THE PLACE OF FUNGI IN MODERN MEDICINE.*

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In the above title the significant words are two, "fungi" and "modern." I shall at once proceed to discuss fungus disease as a whole, and toward the end of the paper shall indicate which developments are modern, or at least promise to lead to results which were not possible in the past.

More and more, and year by year, the average medical man is realizing that fungi at least occasionally play a part in human disease. The pathologist informs him over the cadaver that his case of vertebral osteomyelitis was caused by actinomyces. In the laboratory, he tells him that his case of meningitis was caused by a yeast, and then the dermatologist advises him that the omnipresent, bothersome cracked toes or even an eczema on the dorsa of his feet were caused by fungi and that the infection passed under the euphonious name of dermatophytosis. He is now quite aware that there is smoke in the air and that, after that, there must of course be some real fire at the bottom of it. This much he readily concedes, but he needs and deserves more. The question is how much fire and how to get at it.

Too, the general medical man is quite aware of the obstacles in the way of making diagnoses of fungus infections, besides the elimination of fungus factors as possibilities in a differential diagnosis, and that the hazards stretch not only through the clinical

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domain but extend also beyond the frontier into laboratory territory. Indeed, I feel that the short-comings are much more serious in the laboratory than in the clinic; most of the fungus infections are of the subacute or chronic type which as a class are the more difficult to diagnose, which bear more or less close resemblance to tuberculosis, and which the laboratory man ought to shed more light upon. Most laboratory men will honestly confess that they have little or no training in mycology and that they approach such problems with a great deal of hesitation and unwillingness, just as the average practitioner confesses that he has not mastered dermatology and otology to the extent that he has the other specialties.

The explanation for these delinquencies is not hard to find. Both in the clinical and in the laboratory realms, fungus cases occur far less commonly than the bacterial ones; indeed, it is certain that they will never attain the importance of the bacterial infections. Fungi are far less important than bacteria—at least as we know them now. In the second place, mycologic technique and classifications are radically different from bacterial; if anything, they are more involved than the bacterial. This would mean that the laboratory man, to become quite competent, would be obliged to master yet another biologic field. Already he is sorely beset in attempting to keep pace with such diversified fields as modern serology and biochemistry in addition to older established morbid anatomic, parasitologic, chemical and bacteriologic sections. Pathologists just at present are in great demand; many hospitals are on the outlook at the present moment for good men. The result is that in the face of such immediate crying needs something has to go by the board, and mycology is the phase which has had to suffer.

The remedy, likewise, is clear. Not that every pathologist should be expected to at once assume courses in mycology. This is not necessary in the present state of affairs. What is quite feasible, however, and entirely justified, is the establishment of at least a few laboratories in different sections of the United States with staff pathologists who have taken courses and conducted intensive studies in mycology and can render assistance to the clinician when called upon to assist him in his mycologic problems. To come yet closer to the point, actual ways and means, what we need is a liaison between the first-class clinician and first-class mycologist, the former supplying data and material in a consistent, uniform, systematic way, and the pathologist working up the materials and advising with the clinician. Neither clinician nor pathologist can work alone, they must go hand in hand. Beginnings of this sort should be made in our larger, including tuberculosis, centers. I hear the clinicians inquiring how they can investigate their cases of pulmonary disease and detect the fraction of them at least that are not of tuberculous causation.

The considerations in mycology are not purely academic; indeed,

there is a very practical aspect to the situation. For a long time, it has been known that iodin and the iodids are specific in many fungus infections, and fungus infection extends over a long range of organisms, all the way from the delicate streptothrices, which are so closely related to the tubercle bacillus, through the yeasts and fungi imperfecti to such specialized members as the aspergilli, for instance. The Roentgen rays, likewise, have achieved brilliant results in many fungus infections. With the advent of modern intravenous therapy the therapeutic field has opened up yet more widely, and now that it has been demonstrated that iodin can be administered intravenously in such amazing doses the urgent necessity of identifying fungus cases and of giving patients the benefit of specific fungus treatment is all the more emphasized.

The foregoing applies to conditions in the United States. It also applies to most other parts of the world. But France, Italy, and some of the South American countries with Latin affinities constitute outstanding exceptions. In these countries there is an enormous literature on mycologic subjects; these countries are far ahead of the English- and German-speaking ones.

**Incidence.** After these introductory remarks, let me pass to a consideration of the frequency, as we know it today, with which the various organic systems are likely to be found infected by fungi. It will be observed, as we go along, that frequently it is not so much the fungus affection but the recognition that is rare.

Speaking in general, fungi have a predilection for the same orders of body tissue as the tubercle bacillus. Thus, fungi are rarely, if ever, found in heart or skeletal muscles, or in the pancreas. They are best known on the skin, in the lungs, bones, and after that scatteringly in other organs, such as brain, kidney, spleen, liver, and so forth. Most of the infections are local, confined to the skin, lungs, or bone, as the case may be. Notoriously, however, blastomycosis, sporotrichosis, coccidioidal granuloma, and actinomycosis may become generalized.

In the succeeding paragraphs the attempt will not, could not, be made to indicate the full extent to which the different systems become parasitized by fungi, but simply to offer outstanding illustrations and type cases which will serve to bring home to the physician at large concrete examples of what may be expected to crop out in his experience from time to time; that is, to what extent he must be alert to pick out the occasional instances of fungus infection.

**Generalized Cases.** In order to prevent tiresome repetition under each of the different systems to follow, let us recall that actinomycosis, blastomycosis, sporotrichosis and coccidioidal granuloma notoriously become generalized, and that practically no organ or tissue may escape secondary involvement. In actinomycosis, it is generally known that the primary focus is usually in bone. In blastomycosis and sporotrichosis, it is most commonly in the skin.

In coccidioidal granuloma, there is an undercurrent of feeling that it is frequently a primary pulmonary affection; but from the case reports to date it would appear that the skin is the primary site in most cases. Other fungus species may give rise to secondary lesions, but those just mentioned are the most important.

In the sections to follow, instances of primary involvement will be selected for the most part.

**Respiratory System.** To enumerate all of the fungi which have been claimed as pathogens in this system would be meaningless. Suffice it to say that practically all of the fungus orders are represented, extending from the thread organisms all the way up to such highly organized ones as the aspergilli and the mucors. The latter are indeed the more spectacular and attractive cases; but from the practical standpoint the streptothrices and blastomycetes are the important members. Monilias are responsible for many cases of bronchitis and asthma, as has been brought out by Castellani[1] and Steinfield.[2] Nathan[3] has remarked that patients are commonly sent to a sanatorium where in time they acquire tuberculosis, so that the course of the case ultimately confirmed the erroneous diagnosis.

Both American and foreign authorities are agreed that in most cases fungus infections of the lungs are clinically indistinguishable from tuberculosis and that the only hope of identifying the fungus cases is through laboratory means. This is an important point to keep in mind. Mendelson,[4] in reporting cases of pulmonary mycosis and spirochetosis, even went as far as to insist that tuberculosis can only be ruled out by animal inoculation; this is of particular importance to the laboratory man and finds expression because many of the streptothrices are acid-fast, may assume a beaded form, and thus closely resemble tubercle bacilli in stained preparations. Mendelson[5] also appeals to physicians, especially in the tropics, to rely more on laboratory tests and less on physical signs. Thus, in 100 pulmonary cases which he reported, 5 per cent were caused by fungi, 23 per cent by spirochetes, and the remainder were tuberculous; tubercle bacilli were identified only in 10 per cent of the latter. The importance of accurate diagnosis comes to us with special force when one recalls that the iodid therapy which is contraindicated in open pulmonary tuberculosis is sometimes a specific in the fungus cases.

A further point of tremendous importance to the laboratory man, and one which occasions much puzzlement, is the determination of pathogenicity. From such material as sputum, indeed even normal mouths, it is only to be expected that various forms of fungi will be isolated. Indeed, there is a proper skepticism as to the pathogenicity of most of the species for which such a property has been claimed. There can be no doubt that the list of valid pathogens should be much shorter; but, of course, it will never be possible

to state just what proportion of species is pathogenic and which commensal. We can say, however, that where the attempt has been seriously made it has been possible to satisfy all of the postulates of Koch. Magalhaes,[6] for instance, has proven Oïdium braziliensi as a pathogen by injection into guinea-pigs; he also reproduced the human disease in a monkey by exhibiting the fungus by inhalation. All organs showed fungus, especially the lungs. He stated that the symptoms in his cases were like those of tuberculosis except that there were no night sweats.

To cite a concrete example of pulmonary mycosis, Callender and Coupal[7] have described a case of nocardiosis secondary to inhalation of a chicken vertebra into the lung. It would be possible to multiply the reports of interesting cases which attest the definiteness and importance of fungus infections of the bronchopulmonic apparatus (Lapham,[8] Nicaud,[9] Hamman[10]), but we must pass to the other systems.

**The Digestive Tract.** This certainly ranks next in order of importance. Probably the best known illustration of a digestive tract mycosis is thrush, and also the one which is most thoroughly established as an instance where fungi are unequivocally pathogenic. Up to a few years ago, tropical sprue seemed almost established as due to Monilia psilosis. Of late, it has been severely questioned. However, this affection is comparatively uncommon in continental United States and need not be dwelled upon. Yeast cells, however, have long been intriguing as met so commonly in the intestinal tract in chronic diarrheal states. They have been studied in pellagra, in the sprue already quoted, pernicious anemia and yellow fever. It cannot be stated, however, that anything definite has been attained in these states. A recent paper by Fleisher[11] and Wachowiak, entitled "The Relation of Fungi Imperfecti to Diarrheal Conditions" is an example in point. Just to indicate the diversity of forms under which fungi may produce affections in the digestive tract, let me subjoin the following citations. Chronic monilial infection of the tongue, as reported by Shelmire[12] and by Zeisler;[13] favus of the tongue by Sequeira,[14] patches of red or black hairy villi on the tongue caused by torula or streptothrices, by Alvarez[15] and myself.[16] Calculi have been known to develop in connection with these thread accumulations in the salivary ducts (Kapsenberg[17]); the pathology is analogous to that of the well-known calculi which occur in the lachrymal ducts, which are also referable to clumps of tangled thread organisms.

With the exception of the widely generalizing fungi previously mentioned, the wall of the gut tract as well as the liver and pancreas appear to be seldom infected by fungi. Just at present microscopic sections are lying on my table in which actinomyces were identified by Dr. G. M. Robson of our pathologic department. They appear in the lung and liver of a boy who had been operated upon

for appendicitis; the fungous nature of the appendiceal disease had not previously been recognized or suspected. Foulerton[18] has described Streptothrix hominis III and IV in 2 cases of appendicitis, and a lesion of the esophagus has been referred to puncture by a spine of grain which carried with it one of the actinomyces (Langer[19])

The well-known fact that commercial yeast at least acts as a laxative attracts yet more attention to the persistent reports of chronic diarrheas associated with yeast cells in the stool. Scalas,[20] in an examination of the sputum and stools of 50 cases. reported an oïdium in 7 of 11 cases of digestive trouble. Wood[21] has recently reported experiments which he thinks incriminate Monilia psilosis as one of the causes at least of pernicious anemia, but this has recently been disputed by Nye, Zerfas and Cornwell.[22] The organisms were recovered only from the gums, not from the granulation tissue at the apices of the teeth.

Details concerning thrush are out of place here. Perhaps the only point that is justified is that this disease, while a clinical entity, is not an etiologic one. Indeed, no less than 18 different organisms have been catalogued by Castellani[23] in his Milroy lectures. Oïdium albicans is probably the most common offender, but after this three other oïdiums, a saccharomyces, a hemispora, a willia, an endomyces, and no less than ten monilias find place. Perhaps this is one explanation of why all cases of thrush do not respond promptly to boric acid medication. A further practical point is that, when present in the mouth, the infection may also be present elsewhere. Thus, it has been found frequently enough in intertriginous positions on babies, indeed, there are instances where the original infection was cutaneous and where the mouth involvement has been the secondary one. Meyenburg[24] reports thrush fungus in gastric ulcers. A fatal case involving the skin, lungs and nails is reported by Christison,[25] and Riemschneider[26] reports fatal bleeding as the result of the erosion of a bloodvessel (esophagus) by thrush.

**The Genito-urinary Tract.** Except for the widely generalizing fungus infections, this tract does not appear to be commonly parasitized by fungi. There are several accounts, however, a recent one by Rhamy,[27] where yeast cells have been passed in large quantities in the urine. It is quite possible that this is not a case of true blastomycosis as indicated in the title, but that it is an example of semipathogenicity, the organisms not actually invading the tissues of the host. The situation is probably analogous to the well known aspergillus infections of the ear and the lachrymal ducts already cited where the organisms accumulate and produce their disturbances mechanically—simply as the result of their mass. Instances of black urine and red urine have been reported in which more or less highly pigmented yeast cells were at fault. The red cases have been erroneously mistaken as instances of hematuria. Streptothrix urethritidis has been described in "many" cases of prostatitis by

Schwartz and Cancik.[28] Encouraging results were reported from the use of a vaccine prepared from these cultures.

**The Nervous System.** I do not know of any instances where the peripheral nerves or the substance of the spinal cord has been affected except by extension from a contiguous osseous infection. There are several instances of infection, apart from the well-known actinomycosis and blastomycosis, in which the brain parenchyma has been involved. In infection by cryptococcus the organisms extend to the spinal fluid; most important as a diagnostic opening. I have had close contact with one of these cases through the kindness of Drs. Walter Freeman[29] and Frank B. Lynch. The symptoms are those of meningitis, and the disease is quite undiagnosable except by finding organisms in the spinal fluid. This is very readily done, and Lynch and Rose[30] have reported a case which was diagnosed before necropsy, because they had the acuteness to distinguish yeast cells from degenerate red blood cells. The organism induces myriads of minute, very characteristic mucoid cysts in the brain.

Actinomyces asteroides[31] has been reported as responsible for a number of suppurative lesions of the brain, but numerous other thread organisms have also been scatteringly met.

**Eye.** Gifford's[32] papers contain extensive data on sporotrichosis of the eye and on mycosis in general; likewise, Landrieu's[33] thesis.

Aspergillosis of the cornea has been reported by de Schweinitz.[34] Lachrymal calculi have long been known as due to massive entanglements of Actinomyces foersteri[35] which occlude the duct and may lead to secondary infection. This species is eminently benign, it does not have the significance that actinomyces have as ordinarily thought of.

**Ear.** The only fungus affection of which I am aware in this position is a more or less mechanical obstruction by aspergilli. The organism usually does not invade the surrounding tissues, but simply acts as an impediment. There was a small epidemic of otomycosis in Florida following the hurricane[36] of September, 1926; it appears that heat and moisture favor growth of the fungus, and proliferation is also favored by the instillation of oil. These should, therefore, be avoided. Being a surface affection, iodid of potassium internally has no effect, although it might be tried in the rare instances where suppuration and penetration of the ear drum has taken place. (Koenig.[37]) Besides Aspergillus nigra and fumigatus, Actinomyces cylindraceus (Korte[38]) and Cephalothecium roseum have been regarded as causative.

**Bone.** This claims the interest of the surgeon particularly. Sporotrichosis, actinomycosis and blastomycosis notoriously determine to bone, giving symptoms that are easily confused with those of tuberculosis. A wide variety of fungi has been described producing what are rather uniformly denominated as "gumma-like" swellings of the bone. Indeed, "sporotrichotic gummas" has become the

conventional terminology in that affection. One of the first and, therefore, historic instances of bone infection in human beings by yeast cells affected the tibia, by Saccharomyces hominis (Busse[39]). Just at present I am studying smears and culture referred to me by Dr. David L. Farley of the Pennsylvania Hospital. The pus from an unopened lesion on the skin shows tremendous numbers of sausage-shaped, sometimes budding, yeast cells. At least one case of generalization with fatal outcome is known, due to infection with Cryptococcus hominis.[29] Another instance of osseous gummas is referred to Cryptococcus breweri.[40]

**The Integument.** Here we come upon a field literally ridden with fungus infection, quite understandable. It is impossible to shop even rapidly through the entire list of species; I shall at once pass by the ordinary ringworm of the scalp and the banal tinea circinata, sycosis, and so forth, but must pause long enough to emphasize the most recent addition to, or better recognition of, fungus expression upon the skin. I refer to dermatophytosis.

In short, this is nothing more nor less than a fungus infection which, first, is superficial (that is, excludes deeper affections like blastomycosis) and which, secondly, generally has an affinity for intertriginous positions. This, however, is not always the case; and then the diagnosis is rendered correspondingly difficult.

The general practitioner ought to diagnose dermatophytosis for himself from the eczema with which it is likely to be confounded—he will be served best in this by its localization; that is, usually intertriginous position. Once he suspects dermatophytosis, he can check up in the following way: first, determine whether the margins are sharply outlined; if so, this very strongly fortifies the diagnosis. Second, is there a delicate collarette of epiderm extending around the margin? Again, this is helpful toward the diagnosis. Finally, the direct examination of scrapings under the microscope is often a final and unequivocal answer to the question. This is a very simple laboratory procedure (Weidman),[45] really, it is an office examination rather than laboratory, and one which should be applied by all those who wish to keep abreast with modern practice.

The importance of dermatophytosis will come home to you when I tell you that 67 per cent[41] of a university student group were found to be affected by the disease in the form of ringworm of the toes. The well-known "jock-strap itch" and ringworm of the axilla also come in the category of dermatophytosis.

**Therapeutics.** If there is any one most useful agent in the attack upon fungus infection it is iodin. This has been recognized for many years; not alone as a local remedy but also internally. It can be administered both in the form of potassium iodid and Lugol's solution. It has been most valuable in blastomycosis and in miscellaneous surface infections, but occasionally brilliant results are secured in actinomycosis and even in other more refractory fungus

infections. With the advent of the Roentgen rays, success became even more frequent; most commonly the two agents, iodin and Roentgen rays, have been used in conjunction.

A very practical point in iodin therapy is that the dosage should be large. It is possible, beginning with the usual 5 to 10 grains three times a day, to increase up to as much as 120 grains three times a day, or even more.

It is surprising what large doses of Lugol's solution can be administered intravenously. Shelmire[42] has called our attention to this in this country in treating sporotrichosis. He administers as much as 10 cc. of Lugol's solution, diluted by 100 cc. of normal salt solution, and has had striking results. In France, particularly, but elsewhere, this avenue has been employed in various other fungus infections with excellent results. I know of one failure in the treatment of a particularly obstinate thrush at our University Hospital.

Thallium acetate[43] is another recent addition to our armamentarium; it is thus far confined to treating ringworm of the scalp, having value solely because it produces epilation. Administered orally in the dosage of 8 mg. per kilo of body weight, it causes the falling out of the scalp hair in sixteen to eighteen days. Comparatively uniform success has been reported both in this country and abroad from the use of this most valuable addition to the treatment of fungus disease, but there are dangers and the literature should be consulted before practising it.

In the treatment of the more superficial dermatoses, such as the well-known tinea circinata of children, almost any antiseptic will suffice; the copper penny of the housewife, dipped in vinegar, serves the purpose very well. Tincture of iodin, salicylic acid ointment, 5 per cent, and various other antiparasiticides are effective.

As to dermatophytosis, treatment largely depends upon the part of the body which is affected. On other positions than between the toes, the disturbance usually yields readily upon the application of lotions or ointment of salicylic acid, ammoniated mercury, and other well-known fungicides. There are changes that must be rung when treating this class of fungus affection, depending upon the stage of the disease; thus, when acute, milder applications and when chronic more powerful and stimulating ones. In ringworm of the toes I have come to place most reliance on salicylic acid ointment. This is most conveniently applied in the form of Whitfield's ointment, in which the salicylic acid is represented in a strength of 20 grains to the ounce. It is better to use Lassar's paste as a base because it is more adherent and is less likely to be absorbed by the clothing. Other authorities prefer tincture of iodin, mercurochrome, and various other fungicides. The usual experience in these cases is that there is marked improvement up to a certain point; eventually, all that is left between the toes is a small, circumscribed, white, sodden patch of thickening, which effectually resists further

treatment. As a rule, treatment is discontinued by the patient at this time because the affection is no longer an inconvenience; however, the fungi are still present and constitute a reservoir, a focal infection, which threatens at any time to extend to the dorsum of the foot or elsewhere upon the body. One of the most important problems in fungus affection of the skin today is a certain cure for resistant cases of ringworm of the toes.

**Tartar Emetic.** Guy and Jacob[44] are responsible for discovering that this drug promises much in the treatment[46] of the hitherto invariably fatal coccidioidal granuloma. Tomlinson has just confirmed this—a laboratory infected case which otherwise would have progressed to a fatal outcome. The drug is administered intravenously, beginning with 3 cc. of a 1 per cent solution and increasing up to 10 cc. Occasionally there is a constitutional reaction, but this must be endured in view of the otherwise absolutely black prognosis in this disease.

**Summary and Conclusions.** The various organic systems have been considered in their relation to fungus disease with many indications that fungi are important in modern medicine.

Among the outstanding modern mycological advances, from the diagnostic viewpoint, we have the waxing rôle of pseudotuberculosis, the ubiquity of dermatophytosis, and the possibility of yeast cells being present in bone abscesses and meningitis. Therapeutically, we have as much or more "modernism" in the employment of the Roentgen rays, and medication with thallium acetate, tartar emetic and iodin intravenously.

As physicians we must recognize that:

1. Almost every organ and kind of animal tissue is liable to fungus infection; none of the specialties, except possibly gynecology and obstetrics, is exempt from concern with this class of disease.

2. The profession, if not already cognizant of a certain though minor rôle of fungi in disease, is not addressing itself seriously or continuously enough to the situation.

3. The physician must depend almost entirely upon the laboratory for the detection of fungus cases, particularly in nondermatologic ones and in such important affections as pulmonary pseudotuberculosis.

4. Therefore, the average general laboratory man is largely at fault for our mycologic backwardness because he is not adequately trained in mycology. There is need for at least a few mycologic centers in conjunction with general pathologic laboratories, regionally distributed through the United States.

5. Modern intravenous and other methods of therapy are reinforcing the honored and efficient iodin and Roentgen ray modalities. These, consequent of course only upon accurate diagnosis, should not be denied to the small but still appreciable proportion of fungus patients.

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## GONOCOCCAL AND PNEUMOCOCCAL VEGETATIVE ENDOCARDITIS OF THE PULMONARY VALVE.

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Two cases of this unusual pathology are herein reported and discussed.

**Case Reports.** Case I.—A woman, aged thirty-six years, was admitted to our service in the Mercy Hospital on August 4, 1927, under the care of a colleague, then in charge of the service. She had had no similar illness before and complained only of severe pain in her right wrist and right ankle. There had been a previous history of infection in the throat and the onset had been characterized by general muscular pain and some arthritis of the smaller joints. The severity of the clinical disease was manifested one week before admission, at which time she vomited and had severe headache. Previous to this illness she had been quite well and had suffered only from measles and scarlet fever in childhood. There was a history of 5 living children, 6 children dead in infancy and 4 miscarriages. Her confinements had been in no way complicated and were stated to have been normal in every instance. Since the second day of her clinical illness, the skin had been blotchy on the arms and legs and there were definite herpes about the lips.

There was an interesting history of rheumatism in this family. Her father had had repeated attacks of rheumatic fever, two sisters and two brothers had also suffered from this disease and the impression received on her admission to the hospital when first examined was that of definite rheumatic fever.

The tonsils showed no gross pathology and the only points of interest, aside from the acute arthritides were the many decayed teeth and the herpes labialis.

She was put upon large doses of salicylate by the bowel, 10 gm. daily for five continuous days, after which salicylates were given by mouth in smaller dose. However, on several occasions subsequent to this course of treatment, she received large doses of salicylate by bowel. We seemed to get the usual response of rheumatic fever to salicylates and at the end of three weeks, the temperature was normal and when taken over by us on the first of September, was looked upon as a convalescent rheumatic-fever patient with no apparent cardiac involvement. There is one interesting diary note made by an assistant, who examined the heart on admission, which states that the aortic and pulmonary first sounds were very indistinct.

After a very brief period, this patient developed an intermittent fever with marked diurnal variation, which at times assumed a remittent type and this continued up until the time of her death, November 12, 1927, a period of about ten weeks. Repeated blood cultures showed no bacteriemia. The blood was also tested for malaria, there being some suggestion of estivo autumnal fever, particularly in the presence of a palpable spleen and here the findings also were negative. Two catheterized specimens out of nine examinations of urine enabled us to eliminate the possibility of a pyelitis. The leukocytes ranged in an ascending curve from 12,800 to 20,400 with a corresponding increase of polymorphonuclear leukocytes extending over a period of ten weeks. This patient from the start had almost daily vomiting, which we were unable to help or find the cause of. The oral hygiene was fair except for the old tooth roots. The right ankle and the right wrist presented a focal arthritis, particularly the wrist which suggested a lesion of Neisserian origin, but a pelvic examination made by the gynecologist showed these organs to be normal. After a study of six weeks we were able to find infected teeth as the only possible foci of infection. A few days later, when our working diagnosis was recorded as septicemia, there developed over the precordium definite adventitious sounds, both in the mitral and aortic areas and over the base of the heart a rub, strongly suggesting pericarditis. This development, with the presence of a capillary pulse, made us then feel that the patient was suffering from a bacterial endocarditis of a subacute type. Subsequent study went to confirm us in this opinion. The blood pressure on two occasions was 108 systolic, 72 diastolic, and 118 systolic, 66 diastolic. Fourteen weeks after admission the patient died, having developed a unilateral parotitis two days before death. The principal clinical diagnosis was bacterial endocarditis.

At necropsy there was little evidence of the parotiditis or of the arthritis of the right wrist. The principal findings were in the heart. On removing the heart a firm, yellow, finger-like process was seen to protrude from the right heart, out into the pulmonary artery. When the heart was opened, this was found to be the tip of a large solitary vegetation, involving at its base all but a rim of the posterior cusp of the pulmonary valve. The other pulmonary leaflets showed no evidence of pathologic change. The vegetation was ovoid and measured about 2 by 1.5 by 1 cm. Several smaller vegetations were situated on the mural endocardium of the conus about 0.5 cm. away from the larger one, and one of these appeared to be ulcerated. Microscopically, this was confirmed. The smaller vegetations were found to be fairly well organized except at the immediate surface. Gram-

Weigert stains of the large vegetation revealed Gram negative intra- and extracellular organisms which morphologically were identical with the gonococcus. Culture of the vegetation was not made. The base only of this vegetation showed beginning organization. All the other valves were free, save for a few minute sclerotic thickenings on the mitral leaflets. The myocardium showed a mild degree of fibrosis and some cloudy swelling. It was thought in the gross that a wide irregular scarlike area in the left kidney was the result of old infarction, but on microscopic section the only changes were a very slight increase of the fibrous stroma and a few organized and hyalinized glomeruli, together with some sclerosis of the vessels. The only explanation that remained was that it was the result of vascular sclerosis and that gradual occlusion of a moderate-sized vessel had occurred. The liver was extremely large, weighing 2700 gm., and aside from a fatty infiltration showed a true acute hepatitis, with areas of infiltration by polymorphonuclear leukocytes and lymphocytes. The spleen was large and flabby and of the toxic degenerative type. The internal genitalia showed a bilateral cervical laceration and a chronic salpingitis. The latter is most interesting in view of the possible Neisserian origin of the disease. But the evidence was not quite enough to convince one that this was the primary focus. The case was summed up thus—"The valvular lesion was apparently one of recent development. The causative factor is probably the gonococcus. Clinically the case resembled in some respects one of subacute bacterial endocarditis."

Case II.*—A man, aged sixty-eight years, was admitted to the hospital on May 17, 1923, in a semicomatose condition. He had been found lying in a shed and was brought in by the police. No other history was obtainable.

Physical examination showed an undernourished individual, a few moist râles at the bases of both lungs, some lateral enlargement of precordial dullness with a systolic murmur at the apex and accentuation of the second pulmonic sound and marked edema of both lower extremities. Blood pressure was 102 systolic, pulse 90 to 138, temperature not given. He was catheterized and relieved of 26½ ounces of urine. He died a few hours after admission.

The principal autopsy findings were acute lobar pneumonia (left lower), acute vegetative pulmonary endocarditis (pneumococcic) and acute verrucous mural endocarditis (streptococcic), and acute suppurative cerebrospinal meningitis (pneumococcic). The vegetation on the pulmonary valve was the point of especial interest. *In situ* this vegetation plugged and occluded, in death, the orifice, a large sessile soft mass, unorganized and partially necrotic, measuring 3.4 by 2.2 by 2 cm. and attached to the anterior cusp and, save for a narrow margin at the base, involving the entire cusp. Although the base of the vegetation was on the under surface of the cusp, the bulk of it was directed upward into the pulmonary artery. The mural endocardium adjacent showed several small vegetations. Smears and cultures of the large vegetation and of meninges showed pneumococcus. Culture of the mural vegetations showed a hemolytic streptococcus.

**Comment.** The things worthy of note in these cases seem to us twofold; first, the comparative rarity of acquired pulmonary valve lesions, and second, the probable origin of the vegetations, from a bacteriologic view point. The point of first interest is the rarity of such lesions. Of 24,000 consecutive admissions to the Johns

* By courtesy of de Wayne G. Richey, M.D., sometime pathologist to Mercy Hospital.

Hopkins Hospital, there were only three who showed signs of pulmonary regurgitation.[1] Figures on stenosis are not available, but though more frequent in its occurrence, stenosis is so uniformly of the congenital type that mention of acquired stenosis could not be found. At the Mercy Hospital, between the years of 1910 and 1926, there have been 1192 autopsies. Of these, 18 were in cases of acute endocarditis (including cases of acute and recurrent endocarditis). Only 2 previous cases (0.16 per cent) showed vegetations on the pulmonary valve and one of these was associated with vegetative endocarditis of all the other valves. The other was Case II of the present paper. In this older case, the pneumococcus was isolated, and the lesion was associated with a lobar pneumonia and a pneumococcic meningitis. Incidently there were in the Mercy group[2] 2 cases of gonococcic endocarditis, neither of which involved the pulmonary valve. Autopsy records at the University of Pittsburgh from 1908 to 1924, exclusive of the Mercy group, showed the following results. Of 803 autopsies, the pulmonary valve showed two acute vegetative or ulcerative lesions, one of which occurred on the pulmonary valve alone. It was noted that each of the acute lesions was associated with a congenital lesion or with an acute infection. The percentage of acute lesions in the University group was 0.25 per cent.

The etiology in the first case is not definitely proven; that in the second case quite definite. Bacteria have usually been demonstrated in cases of acute endocarditis, either from the heart's blood or vegetations and these belong almost entirely to the group of pyogenic cocci. Bacteria such as the influenza bacillus, Bacillus typhosus, and Bacillus dysenteriæ have been isolated in rare instances. The most common organisms, however, in order of frequency are, the streptococcus (hemolytic and nonhemolytic), the staphylococcus, the pneumococcus and the gonococcus.[3] The gonococcus falls last in the group but is classed by all writers as one of the common exciting causes of acute endocarditis. Of 176 cases of acute endocarditis, 20 (11.3 per cent) were gonococcal. When the question of pulmonary-valve endocarditis is considered, the situation is reversed. Of gonococcic endocarditis cases from the Johns Hopkins Hospital, 25 per cent showed pulmonary-valve involvement; of all gonococcic cases in the literature (80 in number until 1922) 12.5 per cent were on the pulmonary valve. In all reported cases (1922) of Streptococcus viridans infection of the endocardium, only 7.6 per cent involved the pulmonary; of hemolytic streptococcus, 7.6 per cent; of Staphylococcus aureus, 4 per cent; of Staphylococcus albus, 0 per cent; and of pneumococcus, 4 per cent. It will thus be seen that the gonococcus attacks the pulmonary valve from two to three times as frequently as its nearest competitor for that position, the streptococcus. Of cases collected by Pitt from Guy's Hospital, London, nearly one-half of pulmonary

valve lesions in which a definite infectious cause was ascertained were due to the gonococcus.[4] Barker, of Johns Hopkins, states that all forms of endocarditis in fetal life tend to affect the right side of the heart; in adult life it is only the gonococcic form which shows this tendency.[5]

An interesting comparison of the average duration of the various acute endocarditides is made by Thayer[6] as follows:

| | Weeks. |
|---|---|
| Bacillus influenzæ | 28.0 |
| Streptococcus viridans | 23.1 |
| Gonococcus | 10.5 |
| Staphylococcus albus | 6.8 |
| Staphylococcus aureus | 4.5 |
| Pneumococcus | 4.3 |
| Streptococcus hemolyticus, less than | 3.0 |

It will be noted that Thayer brings what is usually termed the subacute type into the group of acute endocarditis. In this, we have concurred throughout this paper, believing them all to be variations of the same type of pathologic process. The point of especial interest in connection with the present case (case one) is the fact that the duration of our case from the onset of septicemic manifestations was just about ten weeks, or the average time of the gonococcic form of the disease. Also, on further study of the table, it is noticed that the difference between this and those most nearly approaching it in duration is quite wide, the green streptococcus cases lasting about twice as long, the staphylococcus cases only about half as long.

Differences in the morphology of the vegetations occur and have some significance in identifying the type of infecting agent. Vegetations vary in size from pin-point to those occluding a whole valve orifice. Two types deserve mention; first, the vegetations of subacute (Streptococcus viridans) endocarditis, though occasionally large, are usually rather small and multiple. They occur most frequently on the mitral valve (two-third of cases), and the aortic valve, or both, and tend to extend upward onto the wall of the left auricle. They are almost invariably engrafted on old sclerotic valve lesions. Second, staphylococcus, pneumococcus, and gonococcus vegetations are larger, less organized, and often pedunculated. They are frequently associated with ulceration, rupture, or the formation of mycotic aneurysm.[7] Of 20 cases of gonococcic origin at the Johns Hospkins Hospital, 19 showed large vegetations and only one, small ones.[6]

In view of the foregoing discussion, it seemed possible to us to eliminate certain etiologic factors from our first case: (*a*) Influenzal endocarditis is quite rare, for, few cases could be found in the English literature. The present case had no preceding influenzal history and the duration of the disease was too short. Arthritis is

not described as associated with the influenzal form. (*b*) Pneumococcic endocarditis is too brief an illness for our case (though at the time of writing there is in the hospital a case showing pneumococcus in repeated blood culture for the past six weeks), and there is no antecedent history of pneumococcic infection. But most important is the repeatedly negative blood cultures. (*c*) Staphylococcic endocarditis can, we believe, be eliminated by the absence of pyemic manifestations, the sterile cultures, and the duration, which is much too long. (*d*) Rare forms, such as typhoid and dysentery, seem most unlikely and there is no suggestive evidence in their favor. This leaves but two remaining types to be differentiated, namely, the nonhemolytic streptococcic form and the gonococcic. We sum up the evidence for and against each in the ensuing paragraphs.

In favor of the nonhemolytic streptococcus in our case are the following: The rheumatic type of history and history of rheumatism in the family; and the fact that this is comparatively the more common form. Whether the early response to salicylates is evidence of streptococcic infection is open to debate. Arguments against the Streptococcus viridans, as an etiologic factor, are: The relatively short duration of the illness; the repeated sterile cultures; the large size of the vegetation, and the absence of embolic phenomena. In favor of gonococcic endocarditis, the outstanding points are: The duration was (almost too remarkably) the exact average duration found for this disease; the pulmonary valve was attacked, the valve so much more frequently involved by the gonococcus than by any other organism: the vegetation was large; the lesion was preceded by an arthritis that at least in one joint was of a destructive nature; the repeatedly negative blood cultures in the presence of such an intense process points to the gonococcus rather than any other organism: the presence of chronic salpingitis, though not certainly due to the gonococcus, is suggestive; the numerous miscarriages and the early death of several of her children point in the direction of venereal disease; and finally, the presence of Gram-negative intracellular diplococci in the vegetation points strongly to the gonococcus. Unfortunately, no direct smear was made; the examination for organisms being made on sections of the vegetation stained by the Gram-Weigert method. Arguments against the gonococcus are: the relative infrequency of its occurrence (11.3 per cent of 176 cases of acute endocarditis[6]), and the absence of a definite acute focus of infection.

**Summary.** 1. Two cases of uncommon cardiac pathology are presented and discussed.

2. The etiology in one case is culturally positive; the other analytically and presumptively definite.

3. The clinical diagnoses were correct for gross pathology of the endocardium, but not for the valve involved.

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## BILATERAL ANEURYSMS OF THE COMMON ILIAC ARTERIES.

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A CASE of bilateral aneurysm of the common iliac arteries is herewith reported, which is noteworthy on account of its extreme rarity as well as for some clinical facts which permitted the recognition of one of the aneurysms intravitam.

**Case Report.** M. L., aged fifty-eight years, male, white, married, Austrian by birth, real estate operator, was first seen at his home on May 26, 1928. His chief complaint was severe pain in the lower abdomen, vomiting, extreme weakness and inability to empty his bladder. His mother died from a cancer (organ involved not known) and one brother died at the age of forty-five years of cancer of the stomach. At the age of twenty-two, the patient had an appendectomy, and nine years ago he was operated upon for hemorrhoids. At the age of twenty-eight, he had an uncomplicated gonorrhea. About three years ago, while driving his car, he was suddenly seized with a severe pain in the left chest and arm. He consulted a physician who advised absolute rest. He then entered a sanatorium where he remained for about three weeks. While there he had several attacks of precordial pain, which promptly yielded to inhalations of amyl nitrite. On the day of his discharge from the sanatorium he had an unusually severe attack accompanied by staggering gait to the right, double vision and weakness of the left arm. He entered the United Israel-Zion Hospital for further study on December 6, 1925.

On examination, his heart was reported as slightly enlarged to the left. No murmurs, irregularities or accentuations of A2 or P2 were found. The

pulse rate varied from 65 to 90, and the blood pressure was 130 systolic, 90 diastolic. There were no abnormal findings in the chest or abdomen. There were marked sclerotic vascular changes in the retina. The neurologic findings were: Lateral and vertical nystagmus, cerebellar type of speech disturbance, coarse, jerky movements of the fingers of both hands, with ataxia in the finger-to-nose and heel-to-knee tests more marked on the right. There was marked ataxia on walking, with a tendency to fall backward and to the right. No evidences of pyramidal-tract involvement was present. These findings point to an olivo-pontine-cerebellar disturbance. The pain in the left arm may be thalamic, but an anginal origin must be excluded.

**Laboratory Examinations.** Wassermann test, negative; urine, normal. The hemoglobin was 75 per cent and the red cells were 4,000,000; the leukocyte count, 6800. Chemical examination of the blood revealed normal findings. A Roentgen ray study of the chest showed the heart to be of the hypersthenic type with moderate left ventricular hypertrophy. No deformity characteristic of any valvular defect was observed. The aortic arch was unusually broad and dilated, suggesting a fusiform enlargement due to a loss of elasticity.

During his stay at the hospital, the patient had several severe anginal attacks which yielded to nitrites. His general condition improved, his speech disturbance, ataxia and nystagmus became less marked, and he was discharged from the hospital on December 18, 1925, with the diagnosis of probable pontine hemorrhage, arteriosclerosis and aortic dilatation.

His interval history from the time of his discharge to his present illness was not obtained. On May 25, 1928, at about 4 P.M. he was seized with terrific pains in his lower abdomen as if something had burst. He fainted and his family physician was summoned. The next morning he vomited a coffee-ground material which on examination was found to contain blood. He had not voided in about twenty hours and on catheterization a few ounces of bloody urine were recovered. The patient was in collapse, extremely pale and drenched in a profuse perspiration. His radial pulses were imperceptible and the heart sounds were rapid and feeble. Both a systolic and diastolic murmur were present at the third left intercostal space at the sternal border. His pupils were contracted and rigid, possibly the effect of morphin. The lungs were negative. In the left lower abdominal quadrant there was a tender pulsating mass measuring about 15 cm. in the longitudinal and 10 cm. in the transverse diameter. It extended from about the midabdominal line to the left iliac crest and into the left flank. No bruits were heard nor were any thrills palpated. Rectal examination was negative except for prostatic hypertrophy. A bilateral varicocele was present. A tentative diagnosis of a ruptured or dissecting aneurysm of the left common iliac artery was made. The possibility of an encapsulated hemorrhage was considered, and the patient was advised to enter the hospital. He was admitted on May 26 at about 3 P.M.

The next day the abdominal mass had extended to the left costal margin. There was dullness on percussion over the mass. Free fluid in the peritoneal cavity could not be demonstrated. Pulsations were present and equal in both femoral arteries. On catheterization, about 1 ounce of dark urine was obtained. A surgical consultation was requested and the findings were confirmed and expectant treatment was advised. At about noon that day, while an attempt to estimate the blood pressure in the left popliteal artery was being made, for comparison with that in the right, the patient suddenly screamed because of excruciating pain in his left lower abdomen, went into shock and expired in about an hour. His temperature range was from 97 to 100.6°, hemoglobin 60 per cent and the red cells were 2,320,000. The leukocytes numbered 8000.

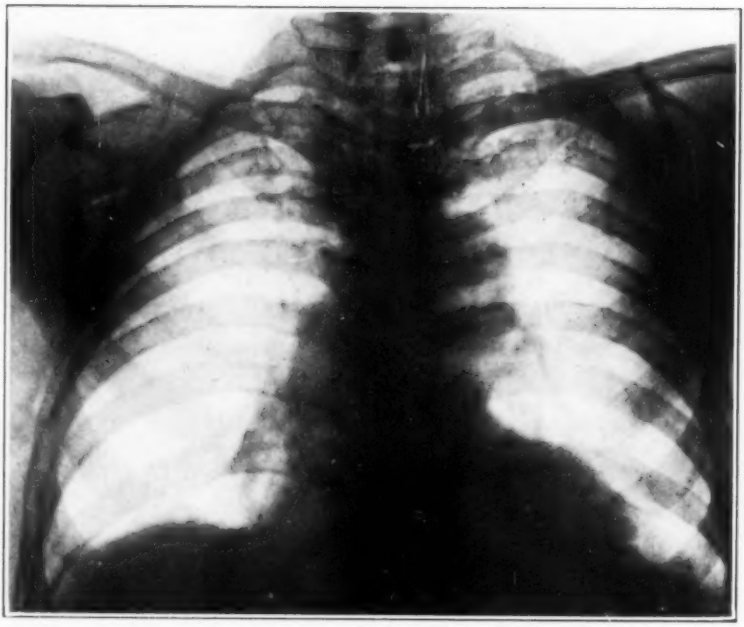

FIG. 1.—Roentgenogram, showing diffuse dilatation of the aorta.

FIG. 2.—Aorta and common iliac arteries opened from behind. Large intramuscular and retroperitoneal hematoma over left aneurysmal sac.

**Autopsy Record.** The body is that of a tall, well-built male. The abdomen is distended and tense. On incision, a small amount of bloody fluid was found in the abdominal cavity. The apices of the lungs are adherent to the chest wall. On section a considerable quantity of frothy fluid oozed from the cut surfaces of the lungs. The heart is enlarged and the musculature of the left ventricle measures about 2½ cm. in thickness. The valves are thin and smooth. The aorta is diffusely dilated from its origin to its abdominal portion. The ascending arch shows just a few normal areas between which are scattered many atheromatous ulcers. There is scarcely any intact intima present. Hard, elevated, almost cartilaginous areas of white fibrous tissue alternate with yellow patches and definite atheromatous ulcers. Most of the fibrous areas are located about the mouths of the intercostals and other arterial branches. Both common iliac arteries are transformed into oval sacs about the size of a fist, the left being the larger. The sacs are partly filled with laminated thrombi. Toward the aortic end of the sac of the left common iliac artery, there is a perforation about the size of a silver half dollar with enormous hemorrhagic infiltrations of the adjacent structures. There is a large tumor mass on the left extending from the diaphragm into the left pelvis. This mass communicates with a similar mass extending into the right pelvis. These masses are covered with peritoneum and are hemorrhagic infiltrations of the iliopsoas muscles and perirenal fatty tissues. The smaller mass is the right common iliac artery surrounded by hemorrhagic infiltrations. The liver and spleen are slightly enlarged, the adrenals are pale with the cortex slightly larger than normal. The kidneys are medium-sized and the capsules strip with difficulty. The kidney substance is pale and the surface granular.

The pathologic diagnosis was atherosclerosis of the aorta with diffuse dilatation and bilateral aneurysms of the common iliac arteries. The left was dissecting and perforated, with infiltrations of the perirenal tissues. Edema of the lungs, cardiac hypertrophy and adhesive pleurisy were present.

This case is of unusual interest because of the presence of bilateral arteriosclerotic common iliac aneurysms. Vascular disease of the aorta and cerebral vessels was clinically and radiographically recognized about two and a half years before the patient's present admission. At that time, abdominal examination did not reveal the presence of any pulsating abdominal masses. The onset of his first symptoms, three days before his death, was probably due to a rupture of the intima of the aneurysm with a dissection of the coats of the vessel. The perforation and retroperitoneal infiltrations which seemed of recent origin most likely occurred at the time of the blood-pressure determination in the left popliteal artery. This procedure probably increased the tension in the aneurysmal sac. The pathogenesis of this double aneurysm is obviously based upon the general sclerosis of the arterial system. There were advanced changes throughout the aorta resulting in a diffuse distention. There were clinical evidences of cerebral vascular disease. No evidence in favor of syphilitic infection could be obtained either from the history, from the postmortem appearance of the organs or from the serology. As a matter of fact, syphilitic aneurysms have a tendency to localize

in the ascending aorta or peripheral vessels. Syphilis seems to spare the larger intermediate vessels. Aneurysms of the descending and abdominal aorta or its larger branches are usually due to atherosclerotic changes.

In reviewing the literature, we have been able to find only two reported cases of bilateral common iliac aneurysms. These cases were reported by Sternberg[1] and by Barber.[2] While aneurysms of the external iliac artery are comparatively frequent, those of the internal iliac are rare, and those of the common iliac artery are still rarer. Matas[3] quotes only 2 cases of common iliac aneurysm among 172 cases of aneurysms of the large arteries of the lower extremities. He refers, however, to the statistics of Crisp[4] who is said to have found 11 cases among 551 aneurysms of the iliofemoral vessels. Wedekind,[5] Hinsdale,[6] Montillier,[7] Maynard[8] and Rivet[9] have each reported unilateral common iliac aneurysms. The case reported by Sternberg[1] resembles our case. Barber's[2] case was found during the course of an exploratory laparotomy. The data concerning the etiology of the reported cases in the literature are rather scanty. Sternberg's case bears the earmarks of a general atherosclerosis in a senile person. There is nothing in Barber's report which could possibly elucidate the pathogenesis of his case. The same applies to most of the cases of unilateral aneurysm of the common iliac artery which we could gather from the older literature. Localization of the aneurysmal distention of the common iliacs is rather unusual, and we are unable to find or offer any explanation for its occurrence in these arteries.

**Summary.** The case presented is that of a bilateral aneurysm of the common iliac arteries of arteriosclerotic origin in which syphilis was definitely excluded. Diagnosis was arrived at by palpation of a large pulsating mass in the left lower abdominal quadrant, which increased in size during the period of observation. There are only two similar cases reported in the literature.

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# TWO CASES OF PERIARTERITIS NODOSA. ONE WITH UNUSUAL MANIFESTATIONS (MENINGEAL FORM).

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Periarteritis nodosa is a rare disease, mainly affecting the small and medium-sized arteries throughout the body. Its rarity is indicated by the facts that it was found in only 2 of the 2035 autopsies performed at the Peter Bent Brigham Hospital and in a recent survey of the literature[1] only 130 cases were uncovered. The disease was first described as a distinct clinical entity by Kussmaul and Maier[2] in 1866 and since then it has been found to exist in a variety of clinical forms. Inasmuch as the underlying, if not the sole lesion, affects the bloodvessels and the injury is very widespread, it is obvious that the symptoms produced will depend upon the particular organs involved. Although vessels of the heart and kidneys are affected very frequently, changes in other organs may predominate and produce the presenting complaints. The patient often complains of pains in the extremities, occasionally in the abdomen, runs an atypical fever with leukocytosis and may develop a number of peculiar symptoms to be classified below.

The specific cause of the disease still remains unknown. However, the febrile course, which lasts from two to several months, and the similarity of the pathologic findings to those observed in Rocky Mountain spotted fever[3] and typhus fever[4] make it very probable that it is infectious in nature. In fact, there are lesions in other infections such as those found occasionally in the small bloodvessels in influenza (cerebral vessels), and epidemic meningitis (skin capillaries),[5] that are not unlike those described in this disease. It is still an open question as to whether periarteritis nodosa is a specific entity or an unusual vascular manifestation of a variety of infections. The latter view was maintained by Gruber,[6] who believed the arterial lesion to be an allergic phenomenon resulting from different infectious agents. The great rarity of such lesions in the many infections that exist and the uniformity of the pathologic findings, when they are seen, make us lean toward the specific nature of the disease.

The particular symptoms and the predominating involvement of certain organs have led to the classification of the following

types of the disease: renal, cardiac, abdominal, neuromuscular, cerebral and dermatologic. The renal type may run a course similar to a vascular nephritis, with symptoms of hypertension, renal insufficiency and failing vision. Other cases may suggest infarction with hematuria. The cardiac type results from a predominant involvement of the coronary arteries. Here, the clinical picture is not unlike the ordinary one seen in coronary sclerosis resulting in symptoms of angina pectoris or myocardial insufficiency. In the abdominal type, symptoms and physical signs of an acute abdominal condition are frequently encountered. One can readily understand the difficult position in which the surgeon finds himself when the patient presents the picture of severe abdominal pain, has a fever and a leukocytosis. It is in this type that the antemortem diagnosis is most commonly made, the nodosities being found in the intraperitoneal bloodvessels. The neuromuscular symptoms are usually present to some degree in all types. These consist of pain and tenderness in the muscles and along the nerves of the limbs and frequently are the earliest complaints. The cerebral form is more rare but has been noted by Fletcher[7] and Dickson[8] and in our more recent case. In the case reported by Dickson, the symptoms of an acute meningitis were very pronounced and yet the spinal fluid did not reveal any cellular or bacterial evidence of such an inflammatory condition. Case II here reported however, showed a marked elevation of the polymorphonuclear leukocytes in the cerebrospinal fluid during the active stage of meningitis although no organisms could be discovered in this fluid. Cases of the cerebral group, because of the nature of the disease, sometimes simulate infarction or hemorrhage of the brain.

It is the purpose of this paper to record one more typical case of periarteritis nodosa and to call attention to some peculiar features in the second case.

**Case Reports.** Case I (Med. No. 24855).—A white American man aged twenty-two years, with an essentially negative family and past history, entered the Peter Bent Brigham Hospital complaining of weakness and loss of vision. Eighteen months before admission he awoke with a right facial paralysis. The paralysis cleared up rapidly but his physician found his blood pressure to be elevated. Three months before entry he began to complain of severe headaches and felt dizzy, with these symptoms he noticed progressive loss of vision.

*Physical Examination.* This revealed a thin, pale individual with a systolic blood pressure of 245 mm. and a diastolic blood pressure of 146 mm. The eyes were prominent, the disk margins blurred, the cupping gone and the retinal arteries were tortuous and showed flame-shaped hemorrhages.

*Clinical Pathology.* This showed no very important change except for slight anemia, a leukocytosis of 19,900, a slight trace of albumin in the urine and fairly numerous hyalin and granular casts.

Four days after admission the patient developed severe epigastric pain, a fever of 103.8°, a marked right sided abdominal tenderness and collapsed. He then improved for about two weeks when he suddenly developed

convulsions of a generalized nature. These recurred for four days and then he began to clear up mentally. His leukocytosis persisted, his blood pressure remained high and his eye sight continued to fail. About two months after admission slight edema was noted, purpuric spots were found over the arms and chest and at the same time his blood-urea nitrogen which had remained around 15 mg. per cent slowly rose to 70 mg. per cent. Death with generalized convulsions occurred nine weeks after admission or about five and one-half months after the onset of the presenting complaints.

*Pathologic Report.* An autopsy performed fourteen hours postmortem, limited to an abdominal incision revealed multiple nodules along the course of the coronary arteries, and a branch of the right renal and hepatic arteries. These nodules varied in size from 1 to 4 mm. in diameter and were very firm and fibrous in consistency. On the under surface of the liver in the region of the gall bladder was a mass of blood clot measuring 6 cm. in its greatest dimensions. The clot appeared grossly to have originated from the substance of the liver adjacent to the gall ladder. Microscopically, the above-mentioned dilatations of the arterial walls in addition to mural thickenings and aneurysmal dilatations, showed a heavy cellular infiltration of the wall and surrounding tissue. In the liver adjacent to the organizing blood clot several small arteries showed endothelial-cell proliferation and a cellular infiltration of the vessel walls themselves.

FIG. 1, Case II. A condensed temperature and pulse chart of the entire illness, showing the high fever which occurred at intervals, accompanied by five major chills. The jagged lines represent practically afebrile periods. The low pulse rate even with high fever is a noteworthy feature.

CASE II (Surg. No. 30087).—A retired business man, aged seventy-one years, entered the hospital November 12, 1927, complaining of pains in the arms and legs.

*Past History.* He had had attacks of biliary colic for the past fifteen years. June 18, 1925, cholecystectomy was performed and numerous gall stones were removed. He was in excellent health after this except for occasional pains in the right big toe (question of gout) and slight dysuria and frequent urination for the past ten years.

*Family History.* Negative.

*Present Illness.* Sometime in the late spring of 1927, while in Italy, he had a minor illness for a few days with some generalized aches and pains but no attention was paid to them. He felt quite well after this until August when he began to have troublesome pains in the arms and legs. They grew worse, were intermittent and shooting in character with a feeling of a dull ache between times. There was exquisite hyperesthesia of the skin with this. About September 1 he had to go to bed where he has remained ever since. Upon diathermic treatment the legs improved but the pain in the arms persisted. Looking for a focus of infection both maxillary sinuses were found to be cloudy, especially the right. This was, therefore, punctured but no pus found. October 11, the patient had a sudden chill, temperature rose to 102.6°. The temperature returned to normal in thirty-six hours. Seven days later, October 18, a second chill occurred. On November 1 he had a third violent chill. The temperature rose to 104°, he went into a coma for about thirty-six hours and showed Cheyne-Stokes breathing. During this attack a stubborn hiccough developed which lasted for about one week. At the time of this last chill, a questionable mass was felt in the left upper quadrant interpreted as being the spleen or the left kidney. There was also found a marked leukopenia, the white count falling to 2000 with marked relative lymphocytosis.

Throughout this period, numerous examinations and tests were carried out trying to explain the persistent troublesome pains in the legs and the attacks of chills, but without success. Blood cultures were negative, Roentgen rays of the chest and bones were negative, blood chemical studies were normal. Blood-urea nitrogen was 10 mg. per 100 cc. Phthalein test was 60 per cent. There were no signs of anemia. The urine was negative except for a rare white blood cell. General physical examination was entirely negative except for marked tenderness on pressure of both arms and to less extent of the legs. Patient was eating quite well and except for the pain was quite comfortable.

He was taken to the hospital for more careful observation of the genito-urinary tract. Roentgen rays of the kidney and pyelograms were negative. No organisms were found in the urine from either ureter. Numerous physicians had seen the patient and it was thought by some that prostatic obstruction might possibly be the cause of the trouble and that the mass felt by one observor in the left upper abdomen could have been an intermittent hydronephrotic kidney. Because of this a suprapubic prostatectomy was performed November 21. The day after the operation, the patient was comatose and showed Cheyne-Stokes breathing and a very distressing hiccough again developed and persisted for ten days. November 27 another severe chill occurred, the temperature rising to 103.° It returned to normal in thirty-six hours. Before this chill, the patient had cleared mentally but again became stuporous and irrational directly after the chill. All this time pains in the arms were very troublesome. On December 5, the fifth major chill occurred, the patient grew cold, began to shake and tremble all over. After about a half hour it was over and a semi-conscious state developed.

At this point, for the first time, definite and marked rigidity of the neck was noted. A lumbar puncture was performed and 10 cc. of slightly cloudy spinal fluid was removed. One hundred and seventy-six cells per cubic millimeter were found, practically all polymorphonuclear leukocytes. No organisms were found. During this chill and shortly after it several blood cultures and spinal fluid cultures were made in ascitic, hydrocele and dextrose broth. These and subsequent bacteriologic examinations were carried out by Prof. Hans Zinsser. Antimeningococcus serum was injected intraspinally (30 cc.) and intravenously (60 cc.). It was thought at this time that the patient may have had a meningococcemia during the past

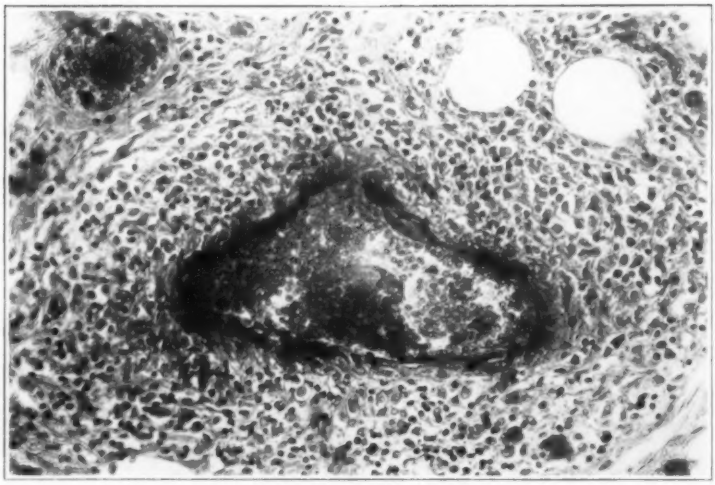

FIG. 2.—Case II. A medium low-power photomicrograph of an esophageal artery showing almost complete destruction of the wall and heavy inflammatory-cell infiltration.

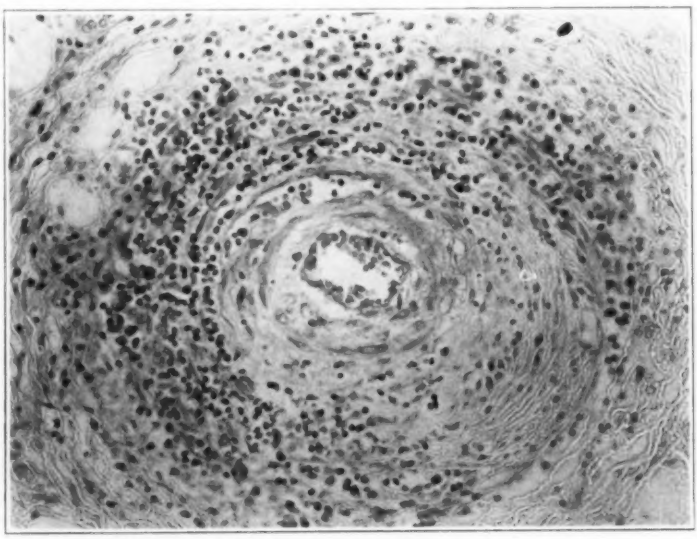

FIG. 3.—Case II. A low-power photomicrograph of a small artery in the center of the sciatic nerve, the wall of which is heavily infiltrated by inflammatory cells.

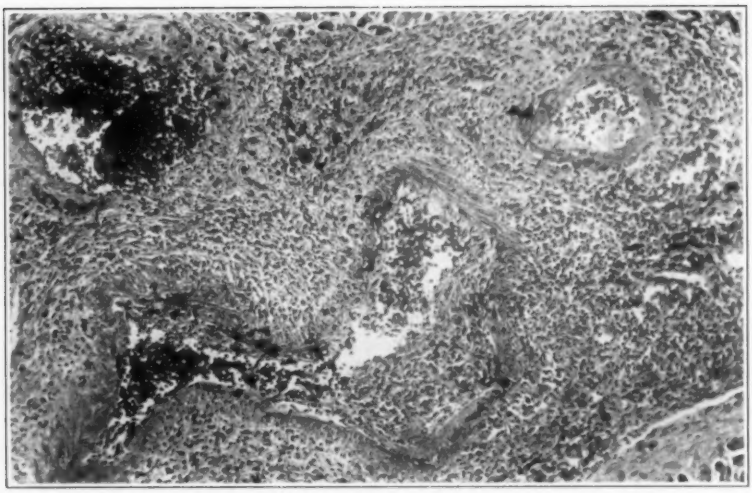

FIG. 4.—Case II. A low-power photomicrograph of pancreatic vessels which indicates the intimal proliferation with partial medial necrosis and heavy periarterial infiltration by a variety of inflammatory cells.

FIG. 5.—Case II. Low-power magnification showing extensive perivascular infiltration with proliferation of the endothelium of the intima and necrosis of the media, in the vessels of the testicle.

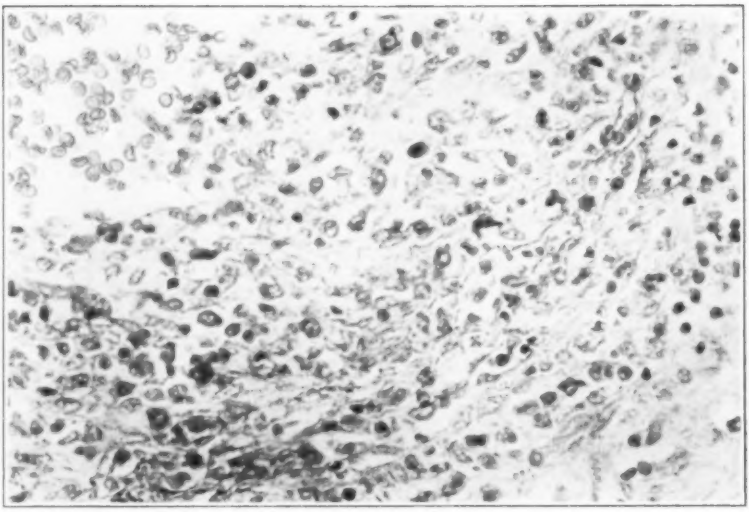

FIG. 6.—Case II. High-power photomicrograph of the wall of an artery of the testicle showing almost complete medial destruction with endothelial-cell proliferation into the lumen.

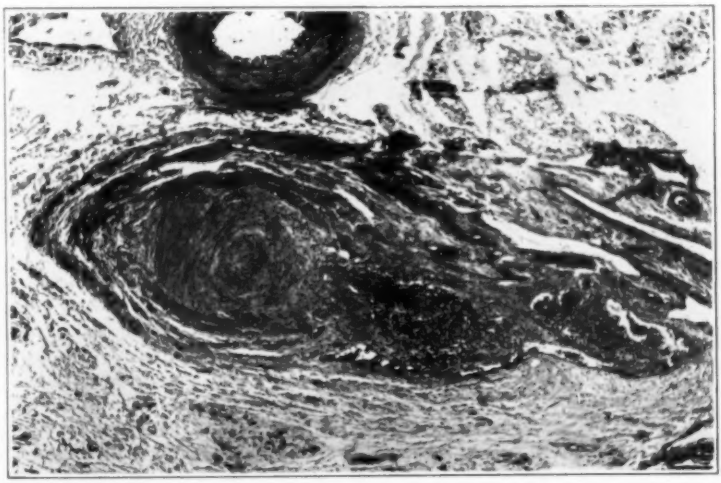

FIG. 7.—Case II. Low-power photomicrograph showing a hyalinized nodosity and inflammatory-cell infiltration in an adrenal arteriole.

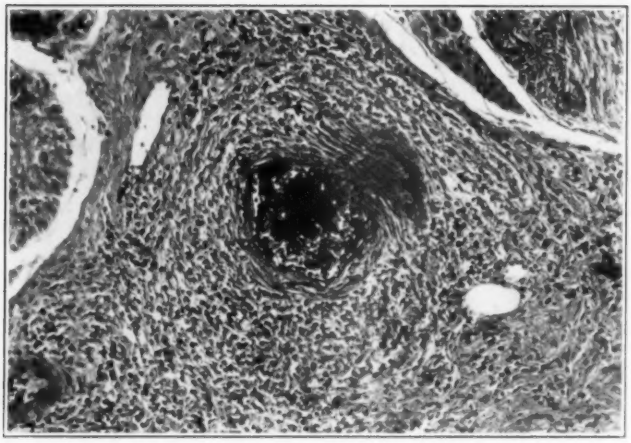

FIG. 8.—Case II. Low-power magnification revealing the perivascular infiltration with some destruction of the vessel wall in the musculature of the urinary bladder.

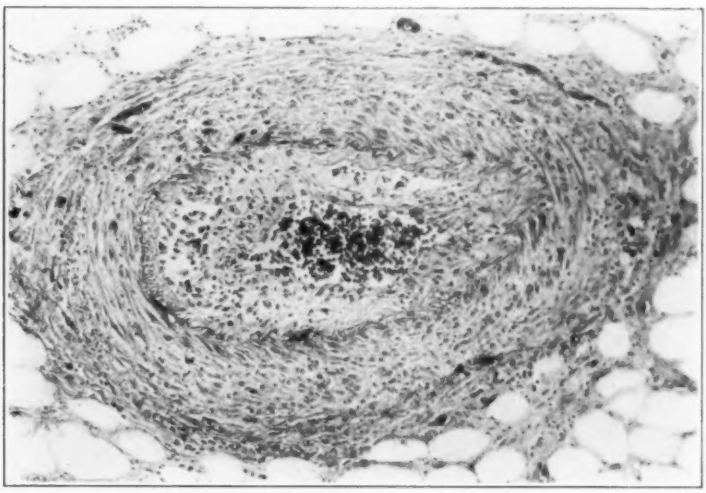

FIG. 9.—Case II. A small artery in the perivesical fat showing marked intimal thickening with relatively little inflammatory-cell infiltration.

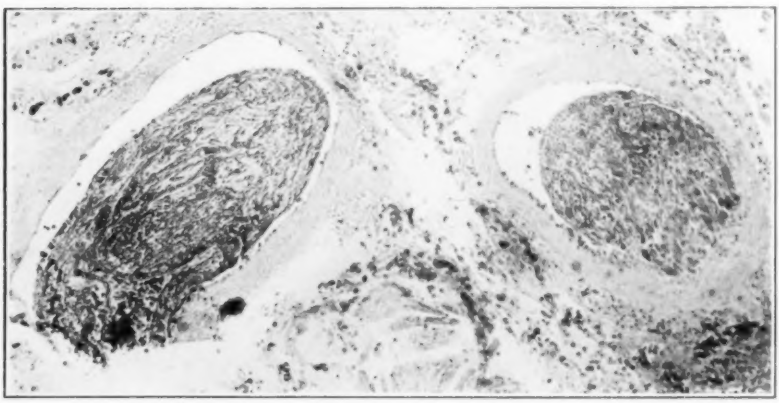

FIG. 10.—Case II. Low-power photomicrograph showing two small pulmonary arteries containing partially organized thrombi.

four months, which finally terminated in meningitis. Three more similar treatments with serum were given both intraspinally and intravenously in the next few days. The cell counts in the spinal fluid were 800 on December 7, 350 on December 9 and 30 on December 19. No organisms were recovered in any of the bacterologic examinations. The temperature remained elevated and after five days gradually returned to normal. During this time the patient was unconscious but after the temperature returned to normal his mind became clearer although frequently he would lapse back into a disoriented state. There were no more chills after this. For a while he improved and began to eat and it seemed as if he would recover. However, he developed several bed sores as he was incontinent most of the time, a large abscess over the lower sacrum had to be incised, he gradually grew weaker, went into a coma and died peacefully January 1, 1928.

Some other points of interest might be mentioned. Blood smears were examined carefully for malaria parasites but none were found. White blood counts, which were frequently made, showed a slight leukocytosis most of the time, from 11,000 to 17,000, even when the patient was feeling fairly well and there were no chills. When the temperature was elevated, the white count was around 23,000. On December 19 the stained blood smear showed a normal number of platelets, but the differential white count showed 18 per cent transitional cells. Electrocardiograms were normal, the blood pressure was about 130 systolic, 80 diastolic. Wassermann test was negative.

Throughout the illness, a source of infection or a localized area of pus was sought for. All our examinations failed to show the cause of the disease. At one time the possibility of brain abscess came up. The ophthalmoscopic examination was negative and Dr. Cushing, who saw the patient in consultation, found no evidence of localized brain pathology. He was treated with antimeningococcus serum because it was barely possible that he was suffering from meningococcemia with terminal meningitis. It is quite definitely known that at times this diagnosis is almost impossible to establish and this treatment offered the hope of a cure if the diagnosis had been correct. The autopsy findings of periarteritis nodosa came as a complete surprise to all those who attended the patient.

*Pathologic Report.* A complete necropsy performed five and a half hours postmortem showed, in the gross, numerous large infarctions of both lungs, a moderately severe bronchopneumonia, some cystitis and a decubitus chronicus over the sacrum. Although a careful search was made, no lesions were found in the gross examination, to explain any of the patients unusual symptoms. The long bones, vertebræ, sciatic and brachial nerves were examined and the brain and spinal cord were removed. It was not until the sections were examined microscopically that the true nature of the disease was understood.

*Microscopic Description.* The microscopic study of the tissues revealed, unexpectedly, a widespread vascular disease, with inflammatory lesions of especial interest in nearly all the organs of the body. These lesions were all very similar in that they all showed varying stages of tissue response to a presumably infectious agent, and that they were all confined to the blood-vessel walls and perivascular areas. In all instances the histopathology corresponded very closely to the vascular changes described in periarteritis nodosa. Because of the similarity of each lesion and the very complete descriptions given by other authors, only a brief report of the microscopic findings will be given.

Involved vessels show considerable variation in size but in most instances it was the small- and medium-sized arteries which showed the more extensive changes. While the principal cellular infiltration was external to the vessel walls, the walls themselves were often partially or completely de-

stroyed and there was a heavy infiltration with endothelial leukocytes, lymphocytes, polymorphonuclear leukocytes and fibroblasts. There was marked loss of cellular definition of the media coats as well as the heavy inflammatory cell infiltration. In many places the weakening of the wall was made evident by the marked necrosis of the media, which in places had reached such a degree that only a few hyalinized muscle fibers remained. A crescentic thickening of the intima due to an endothelial-cell proliferation was a notable feature in many instances; this also was accompanied by infiltration of polymorphonuclear leukocytes and lymphocytes. The intimal thickening was usually more pronounced on the side of most marked medial destruction. In a few of the older lesions, notably the lungs, an occasional organized and partially canalized thrombus was present. The inflammatory process in practically all instances extended out into the perivascular tissues and was characterized by an infiltration with endothelial phagocytes, lymphocytes, polymorphonuclear leukocytes and fibroblasts. Marked congestion in these areas was also frequently seen. Because of the dense cellular infiltration it was difficult to find the bloodvessels of the vasa vasorum, but the impression was frequently gained that there was new bloodvessel formation in the adventitia.

Special mention of the central and peripheral nervous system seems warranted in relation to the unusual symptomatic manifestations. Examination of sections from a great many blocks of brain, spinal cord and the brachial and sciatic nerves revealed scattered lesions of some of the included vessels. While the involved arteries were not as numerous nor as extensive as those in other parts of the body, they were in other respects similar and denoted a periarteritis as well as an arteritis and an endarteritis. Evidence of a healing or a healed meningitis could not be found in a study of numerous sections taken for that purpose.

*Bacteriology Note.* The bacteriology that was done consisted of cultures made from the heart's blood, spleen and meninges, using blood agar, hydrocele agar, and brain broth as culture media. All of the original cultures and subcultures were overgrown with colon bacilli, but no other organisms could be found. Sections from the more extensive lesions were made and stained by Gram's, Giemsa's, Goodpasture's and Levaditi's methods, but no organism nor spirochetes could be found. It must be noted that numerous cultures were made from the blood and spinal fluid during the height of fever and during the active stages of meningitis but no organisms were ever grown. These cultures were made in ascitic, hydrocele and dextrose broth.

**Summary.** The first case reported herein occurred in a young man, aged twenty-two years, and was typical of periarteritis nodosa. It belonged to the cardiorenal type of the disease for hypertension, cardiac and marked renal insufficiency were present. At autopsy, the nodosities along the medium sized arteries were recognized in the gross.

The second case was most unusual. There were repeated severe chills and fever (Fig. 1) with perfectly normal periods of about one week between these spells. Practically the only complaint and the one with which the illness was initiated was painful and tender limbs. This symptom persisted until the end. After a course of three months, clinical evidence of meningitis and coma developed. The spinal fluid findings with a high leukocyte count indicated an active meningitis, but no organisms could be cultured from either the blood or spinal fluid at any time, and no organisms were ever

found in smears. Because the clinical course was similar to the rare instances of meningococcemia with terminal meningitis, the patient was given antimeningococcic serum without any effect.

On postmortem examination typical microscopic lesions of periarteritis nodosa were found in the bloodvessels of almost all the organs of the body. Some of these lesions were acute in nature while others were in varying stages of healing, making the total picture compatible with the long clinical course of the disease. The coronary arteries were particularly spared and the arteries of the nerve trunks were markedly involved.

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# REVIEWS.

BRONCHIAL ASTHMA. ITS DIAGNOSIS AND TREATMENT. By HARRY L. ALEXANDER, A.B., M.D., Associate Professor of Medicine in the Washington University Medical School, St. Louis; Associate Physician to the Barnes Hospital, St. Louis. Pp. 171; 8 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $2.25.

IN the last few years a number of books have been written on bronchial asthma. Their authors have usually fallen into the same errors: an overemphasis of the rôle of hypersensitiveness in the disease and the omission of much important older work. This is the first book in which these pitfalls have been successfully avoided. The author has managed unusually well to keep both feet on the ground in his correlation of the old with the new, so that he may well be forgiven his stand on a few minor controversial points, such, for example, as the inclusion of vaccines only under the head of "Non-specific Therapy." The reviewer does not hesitate to recommend this book to physicians and students as the best on the subject.

R. K.

GROWTH. By WILLIAM JACOB ROBBINS, SAMUEL BRODY, ALBERT GARLAND HOGAN, CLARENCE MARTIN JACKSON and CHARLES WILSON GREENE. Pp. 189; 83 illustrations. New Haven: Yale University Press, 1928. Price, $3.00.

THE series of popular lectures published in this volume was delivered under the auspices of the Missouri Chapter of the Sigma Xi. Each of the five lectures was delivered by a member of the faculty of the University of Missouri.

W. J. Robbins gives the introductory chapter a clear and interesting discussion of growth in general. The course of growth and senescence is presented by Samuel Brody from the viewpoint of mathematical analysis. A. G. Hogan discusses the relations between growth and nutrition, giving timely information on the present status of vitamins and foodstuffs to growth. What determines bodily form is the subject of the chapter by C. M. Jackson. Finally the important subject of internal secretions in their relation to growth is presented by C. W. Greene.

Each of these contributors is a recognized authority in his field.

While the matter is presented in a way comprehensible even to the nonmedical reader, it should be chiefly valuable to the physician who wishes to bring up to date his knowledge on this very vital subject. M. M.

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WILLIAM HARVEY, By ARCHIBALD MALLOCH, M.D. (McGILL), M.R.C.P. (LOND.), Librarian, New York Academy of Medicine. Pp. 103; 13 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $1.50.

TERCENTENARY editions of Harvey's works have already been reviewed in these columns; and now we have, in the attractive form and low price that we have come to expect and appreciate in Hoeber's Biographical Series, a short life based on the author's tercentenary address at Boston. In addition to the briefly told story of the discovery of the circulation, one reads interesting comments on Harvey's continental tours, his intercourse with the witches, his autopsy of "Old Parr," his connection with the College of Physicians and of his other great work, "de Generatione Animalium." This booklet will not, and is not intended to, replace the longer lives by Willis, Power and others. E. K.

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HANDBOOK OF MICROSCOPICAL TECHNIQUE. EDITED By C. E. MCCLUNG, PH.D., Professor of Zoölogy and Director, Zoölogical Laboratory, University of Pennsylvania. Pp. 495; 43 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $8.00.

A DESIRABLE supplement to the volumes of General and Special Cytology, the latter from the same publisher—an association that is emphasized by a similarity of binding—this handbook aims to present precise details of technique of the methods involved.

The short first part, by Doctor McClung outlines for the inexperienced worker approved general methods of preparing microscopical slides. Part two discusses in more detail the following special methods: Microdissection, by R. Chambers; Vital Stains, by N. C. Foot and F. R. Sabin; Bacteriological Methods, by H. J. Conn, F. B. Mallory and F. Parker, Jr.; Botanical Microtechnique, by W. R. Taylor and S. H. Eckerson; Cytological Methods, by C. E. McClung, E. Allen, R. T. Hance, J. W. McNabb and E. V. Cowdry; Embryological Methods, by C. E. McClung and E. Allen; Red Blood Cells, by R. Isaacs; Leukocytes, by E. M. Slider and Hal Downey; Bone, by Paul G. Shipley; Dental Technique, by J. L. T. Appleton, Jr.; Intercellular Substances of the Connective Tissues, by F. B. Mallory and F. Parker, Jr.; Muscle and Electric Organ Tissues, by U. Dahlgren; Neurological Technique, by W. H. F.

Addison, W. Penfield and W. V. Cone; Protozoölogical Methods, by D. H. Wenrich; Fixation and Fixatives, by C. E. McClung and E. Allen; Stains by C. E. McClung and H. J. Conn.

Thus it will seem that the eminence of these contributors guarantees the editor's assumption that the work will be "of interest to workers in bacteriology, botany, cytology, embryology, histology and pathology" and of practical use as well. Where all parts are good, distinctions are especially invidious, but one cannot help but call attention to the sections on microdissection, vital staining, intercellular tissues, and the newer neurological methods, if only for the added convenience that this presentation offers. Overlapping perhaps the field of such books as Lee's "Microtomist's Vademecum" and Mallory and Wright's "Pathological Technique," this book covers a number of topics not included in other works and will be correspondingly welcome. It is difficult to see how it can be omitted from the bookshelf of any biological laboratory or student earnestly concerned with these subjects.

E. K.

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History of Medicine. By Fielding H. Garrison, M.D., Lt.-Col., M.C., U.S. Army. Fourth edition. Pp. 996; 286 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $12.00.

A new edition of this best of all histories of medicine is an important event in medical publishing, and especially so when it has been as carefully and extensively revised as is here the case. A melancholy flavor is added by the author's acknowledgements *zum lezten mal*, but let us hope that as with other artists, operatic and otherwise, circumstances may prove too strong for him.

As compared with earlier editions the book has been somewhat enlarged, but kept within convenient bounds by the use of a slightly enlarged page and smaller font in places and by curtailing the earlier phases to permit a more adequate presentation of the constantly growing "modern" section. Colonel Garrison's specialization in this field peculiarly fits him to do justice to this most difficult of all periods and in spite of the fuller treatment, it is safe to say that its inherent worth could justify an even greater number of pages. The lessons and medical achievements of the World War have been included, also a new chapter on prehistoric medicine, and the Appendiceal Chronologic list and Bibliographic Notes considerably extended. In the newly-written preface one finds an interesting survey of the increasing interest in medical history since the publication of the third edition seven years ago. The author seems to have demonstrated that occasionally it is possible profitably to gild the lily.

E. K.

THE STORY OF MODERN PREVENTIVE MEDICINE. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 295; 9 illustrations. Baltimore: Williams and Wilkins Company, 1929.

THIS volume is a continuation of "Evolution of Preventive Medicine" (1927), which described the subject up to the time of Pasteur. It nevertheless tells a united story of the topics it deals with, so that Laennec, Villemin and others appear in the chapter on causation of diseases; Leeuwenhoek and Redi in the settling of the question of spontaneous generation and so on. We are carried in twenty-nine chapters through all the infectious diseases, then through historical considerations of physical and social conditions of health (ventilation, sunlight, housing, etc.) and finally through some physiological conditions of health, such as goiter, hormones, vitamines and alcoholism.

Written by an acknowledged expert in this field, the description of the progress in our knowledge of the cause, prevention and cure of these diseases may be taken as authoritative. As the treatment is elementary, much will be found by the educated physician that is not new to him, but much more which is both interesting historically and important practically. E. K.

# BOOKS RECEIVED.

## NEW BOOKS.

*Report on Fourth International Congress of Military Medicine and Pharmacy, Warsaw, Poland. May–June, 1927.* By WILLIAM SEAMAN BAINBRIDGE, COM., M.C., U.S.N.R. Pp. 248; illustrated. Menasha, Wis.: Collegiate Press, 1929.

*Nephritis: Its Problems and Treatment.** By T. IZOD BENNETT, M.D. (LOND.), F.R.C.P. Pp. 94; 3 illustrations. New York: Oxford University Press, American Branch, 1929.

*Youthful Old Age.* By WALTER M. GALLICHAN. Pp. 236. New York: The Macmillan Company, 1929. Price, $2.50.

A book by a layman who has apparently attained the philosophy of Rabbi Ben Ezra, and says that he is happier at sixty-seven than he was at thirty years. Those who agree with the author that "life is a sweet potion of labor and love and life is worth living" should be interested.

*Endocrine Diagnostic Charts.* By HENRY R. HARROWER, M.D. Pp. 144. Los Angeles: The Harrower Laboratories, Inc., 1929. Price, $1.00.

*Antenatal Care.** By W. F. T. HAULTAIN, O.B.E., M.C., B.A., M.B. (CAMB.), and E. CHALMERS FAHMY, M.B. (EDIN.), F.R.C.S.E. Pp. 113. New York: William Wood & Co., 1929. Price, $2.25.

*The Normal and Pathological Physiology of Bone: Its Problems.** By R. LERICHE and A. POLICARD. Pp. 236; 33 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, $5.00.

*The Climacteric.** By GREGORIO MARANON. Pp. 425; 19 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $6.50.

* Reviews followed by an asterisk will appear in a later number.

*Oxford Monographs on Diagnosis and Treatment. Volume I: Disorders of Metabolism.** By JAMES S. MCLESTER, M.D. Edited by HENRY A. CHRISTIAN, M.D. Pp. 328. New York Oxford University Press, American Branch, 1929. Price, $100, a set of 10 volumes.

*Volume II: Diseases of the Stomach and Intestines.** By WILLIAM FITCH CHENEY, B.L., M.D. Pp. 280.

*Volume III: The Diagnosis and Treatment of Diseases of the Heart.** By HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Pp. 355.

*Volume IV: The Diagnosis and Treatment of Diseases of the Thyroid.** By JAMES H. MEANS, M.D., and EDWARD P. RICHARDSON, M.D. Pp. 366; 50 illustrations.

*Progressive Medicine. Volume I, March, 1929.* Edited by HOBART AMORY HARE, M.D. Pp. 352; illustrated. Philadelphia: Lea & Febiger, 1929.

*Injection Treatment of Internal Hemorrhoids.** By MARION C. PRUITT, M.D., L.R.C.P.S. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S. Pp. 137; 9 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $3.00.

*Medical Information in Sickness and Health.* By PHILIP SKRAINKA, M.D. Pp. 577. Coward-McCann, Inc., 1929.

A book on household medicine calculated "to bring doctor and patient closer together." The historical notes that introduce some of the diseases are of especial interest.

*The Newborn Infant.** By EMERSON L. STONE, M.D. Pp. 183. Philadelphia: Lea & Febiger, 1929. Price, $2.00.

*Surgical Clinics of North America. Chicago Number, April, 1929, Volume IX, No. 2.* Pp. 243. Philadelphia: W. B. Saunders Company, 1929.

*An Index of Symptomatology.** By Various Writers. Edited by H. LETHBY TIDY, M.A., M.D. (OXON.), F.R.C.P. (LOND.). Pp. 710; 130 illustrations. New York: William Wood & Co., 1929. Price, $12.00.

*Gleanings from General Practice.* By DAVID TINDAL, M.D., F.R.F.P.S. (GLAS.). Pp. 209; 3 illustrations. New York: William Wood & Co., 1929. Price, $2.50.

Tips gleaned from a long clinical experience, calculated to be of use to the young practitioner. Chiefly concerned with medical treatment.

*Transactions of the American Surgical Association. Volume XLVI, 1928.* Edited by JOHN H. JOPSON, M.D. Pp. 503; illustrated. Philadelphia: J. B. Lippincott Company, 1929.

*Clinical Electrocardiograms: Their Interpretation and Significance.** By FREDERICK A. WILLIUS, M.D. Pp. 219; 368 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $8.00.

## NEW EDITIONS.

*The Writing of Medical Papers.* By MAUD H. MELLISH-WILSON, Editor of Mayo Clinic. Third edition. Pp. 184. Philadelphia: W. B. Saunders Company, 1929. Price, $1.50.

A booklet that should be on the desk of everyone writing a medical paper. If, in addition, its precepts could be carried out, even to a 50 per cent extent, the lives of medical editors would be considerably lengthened.

*Tuberculosis and How to Combat It.* By FRANCIS M. POTTENGER, A.M., M.D., LL.D., F.A.C.P. Pp. 275. Second edition. St. Louis: C. V. Mosby Company, 1929. Price, $2.00.

* Reviews followed by an asterisk will appear in a later number.

# PROGRESS

OF

# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

**The Splenic Lesion in Sickle-cell Anemia.**—Rich (*Bull. Johns Hopkins Hosp.*, 1928, **43**, 398) found five such characteristic lesions in the spleens of Sickle that he was able to pick out of 5000 autopsied spleens 62 which showed the same change. Further investigations showed that all these were from negroes and sickle cells were found in all. The lesion is a congenital malformation of the splenic sinuses which permits an excessive escape of red cells into the pulp. Pronounced malformation of the spleen about the Malpighian follicles causes a collection of pools of blood in these areas which later become greatly fibrosed and perhaps calcified, resulting in marked atrophy. The anemia is of a hemolytic type with a development of hemosiderin in the tissues.

**Xanthomatosis and the Reticulo-endothelial System.**—An important correlation of a group of cases of Christian's syndrome (defects in membranous bones, exophthalmos and diabetes insipidus) has been made by Rowland (*Arch. Int. Med.*, 1928, **42**, 611), on the basis of 2 original cases and 12 in the literature occurring in early childhood. He draws certain conclusions as to their microscopic changes, pathogenesis and their relation to the reticulo-edothelial system. There was a generalized visceral xenthomatosis in which many parts of the system show storage, or diffuse hyperplasia in various organs, particularly the bone marrow, lymph nodes and spleen. He considers that lipoids and other substances in the body fluids, becoming pathogenic, irritate the vessel walls with perivascular cell infiltration; the lesions increasing as a result of the progressive blockage of the system with compensatory hyperplasia in an attempt to get rid of the harmful substances. Abnormal congenital pre-disposition has not been proved. He finds no essen-

tial difference between all the forms of xanthoma and Gaucher's and Niemann's disease. The above distribution, exophthalmos, diabetes insipidus, dwarfism and infantilism, are all the result of this pathogenic change acting through the pituitary.

**Relation of the Bone Marrow to Disease.**—In 130 autopsies in which the bone marrow was examined, STAAL (*Inaug. Diss., Groningen*, 1927) found that changes first took place in the lower epiphysis, and that the red marrow persted longest in the upper part of the diaphysis and shaft. In inflammations active hyperemia may appear as soón as two days, to be quickly followed by increase of myeloid tissue and atrophy of the fat cells. Lymphocytic changes are only found in lymphadenoma, but status lymphaticus is not a prerequisite for the presence of lymph follicles. Tumors in the aged are most apt to produce gelatinous degeneration, which also may occur in the cachexia of acute and chronic inflammations. The most marked change occurs in the so-called primary blood diseases and in extensive carcinomatous metastasis or myelophthisis.

**Hypercholesterolemic Splenomegaly.**—An interesting case exhibiting subacute hypertrophic biliary sclerosis with icterus and hypercholesterolemia (1250 mg. per 100 cc.), xanthoma and splenomegaly is reported by DYKE (*J. Path. and Bact.*, 1928, **31**, 173). Both splenomegaly and the xanthomata were considered to be the result of the high cholesterol content of the blood.

## SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

**Dupuytren's Contraction.**—KANAVEL, KOCH and MASON (*Surg., Gynec. and Obst.*, 1929, **48**, 145) say that twenty-nine cases of Dupuytren's contraction are reported which have served as an incentive for a careful study of the normal fascia of the hand and an opportunity for observing the unusual changes which it undergoes in this condition. Seven of these cases had been operated upon previously, some of them more than once and in each case the condition had recurred. The results observed in such cases and the results obtained in the cases operated upon by the authors have impressed them with the importance of wide excision of all the fascial attachments to the skin, to the interfascial septa and to the phalanges. Although in such an operation apparently normal fascia may be removed, these authors do not consider this a disadvantage, but rather an added guarantee against recurrence. Careful dissection and elevation of the skin is done to

avoid trauma and subsequent necrosis. Painstaking effort is taken to avoid injury or division of the digital nerves and bloodvessels which are frequently embedded in the bands of fibrous tissue which draw the fingers into flexion. Skin that is hopelessly involved is excised and replaced by a free full-thickness graft. In long-standing cases with marked contraction of the fingers, the head of the proximal phalanx is excised and the extensor tendon is shortened through a dorsal incision. Active movement of the fingers and hand are followed as soon as the operative wound is soundly healed.

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**Primary Carcinoma of Lung.**—KIRKLIN, PATERSON and VENSON (*Surg., Gynec. and Obst.*, 1929, **48**, 191) declare that in the early stages carcinoma of the lung may be divided into two types with clinical and roentgenological entities: Bronchial, arising in the wall of a first to third degree bronchus, and parenchymal, arising in the substance of the lung. In the bronchial type there is a history of early chronic, persistent cough, not greatly productive, but often associated with hemoptysis or blood-tinged sputum. Usually there is a loss of weight. Unilateral infiltrating density at the hilum is seen in the roentgenogram in some cases, but more constantly atelectasis of a lobe, due to bronchial obstruction is seen. The parenchymal tumor is more latent, but there is definite loss of weight and a peculiarly ill-localized type of pain in the chest. Later the bronchus may become invaded, in which case the lesion resembles the bronchial group. In the roentgenogram it is seen as a round nodule, with infiltrating edges and lying free in the lung tissue. Later it involves the whole or most of a lobe. In the later stages the two types tend to a common type and the actual malignancy is obscured either by pleural effusion or by infective processes. This is associated with dyspnea or the usual evidences of infection. Pathologically the analysis seems to show that the parenchymal tumor is usually an adenocarcinoma, that the bronchial tumor may be either adenocarcinoma or epithelioma, the epithelioma being confined to the bronchus and the lesion is of a high grade of malignancy.

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**Strangulated Left Duodenal Hernia.**—COLEY (*Arch. Surg.*, 1929, **18**, 868) finds that the retroperitoneal hernia is a relatively rare condition, since only 38 reported cases of all types were found by Short in a ten-year period. Hernia into the left paraduodenal fossa is by far the most common variety of retroperitoneal hernia. Forty-three cases of left paraduodenal hernia, which produced symptoms during life, were reported by Short in 1925. The author has added 7 more cases and reported an eighth, bringing the total number to 51. The symptoms are, for the most part, those of intestinal obstruction, but the presence of a mass to the left of the median line is important. Diagnosis is seldom made before operation. Treatment consists in reduction of the herniated intestine, with care to avoid injuring the vessel, which lies in the free edge of the neck of the sac. Partial excision of the sac or obliteration of its cavity, is advisable whenever possible. The condition of the bowel may necessitate resection. The mortality rate after operation has been decreasing. This may be attributed, in part, to more prompt surgical intervention in cases presenting symptoms of intestinal obstruction.

**Cholecystogastrostomy—An Experimental Study.**—Beaver (*Arch. Surg.*, 1929, **18**, 899) states that an experimental study of cholecystogastrostomy was undertaken to determine the effect of bile in the stomach on gastric secretion and mobility as well as the possibility of the biliary tract and liver. Twelve normal dogs were studied in two series of six dogs each. In the first series gastric digestion was studied by the McCann method of fractional gastric analysis for dogs. The emptying time of the stomach was also determined by means of the barium meal and the fluoroscope. Cholecystogastrostomy was then performed with double ligation and incision of the common bile duct. Following recovery fractional gastric analyses were again made to determine whether the bile had any effect on gastric acidity. The results in the first series showed definitely that bile did not have any effect on the acidity of the stomach. The postoperative emptying time was essentially the same as the preoperative. In the second series of dogs gastric analyses were not made, but the same type of operation was performed as in the first series. The dogs were allowed to live under normal conditions for varying lengths of time and were then operated upon to determine whether pathologic processes were developing in the gall bladder and liver. The results of the observations in the second series led to the conclusion that infections of the biliary tract and liver always occur following cholecystogastrostomy. It is suggested that the absence of clinical evidence of such infections does not preclude the possibility that pathologic changes in the biliary tracts and liver are occurring in patients subjected to cholecystogastrostomy.

## THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE NEW YORK CITY,

AND

SOMA WEISS, M.D.,

FACULTY INSTRUCTOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

**Liver Diet and Funicular Myelosis.**—Wolf (*Med. Klin.*, 1928, **24**, 1673) records a case of well-developed posterior lateral column myelosis in a patient suffering from a moderate grade of pernicious anemia in whom the administration of a diet containing 300 gm. of liver per day brought about a complete restoration of the blood picture and a very pronounced improvement in the nervous manifestations. Hearing, ataxia and paresthesia were all greatly benefited by the treatment and the objective signs on the part of the nervous system disappeared almost entirely. He cites a second patient in whom some improvement in the blood picture has already been produced but in whom the treatment has not been sufficiently prolonged to determine whether or not it may be capable of overcoming the symptoms of myelosis although some improvement has been observed within the first two weeks of treatment.

The close relationship known to exist between this form of myelosis and pernicious anemia seems to be further established by the response of the former, as well as of the latter, to the administration of liver.

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**The Use of Galvanocautery for the Destruction of Pleural Adhesions as a Preparation for Artificial Pneumothorax.**—The use of artificial pneumothorax in the treatment of pulmonary tuberculosis is frequently rendered unsatisfactory or impossible by the presence of pleural adhesions which prevent satisfactory collapse of the lung. JACOBAEUS (*Therap. d. Gegen.*, 1928, **69**, 433) advocates the severance of pleural adhesions by means of the galvanocautery for the release of the adherent lung as a preparation to the employment of pneumothorax. He states that the procedure is usually one that may be carried out without undue difficulty. The patient is studied by means of Roentgen ray in order to localize the adhesions. Then a thoracoscope is introduced under local anesthesia at a point usually from one to three intercostal spaces below the level of the adhesions. When the adhesions have then been studied visually through this instrument and accurately located a second thoracoscopic cannula is introduced to permit the passage of a galvanocautery. Under constant direct vision the adhesions are then slowly burned through. Experience shows that the results are more satisfactory and the danger of hemorrhage and subsequent spontaneous pneumothorax are much less when the cautery is used at a temperature just sufficient to cause it to glow a dull red. Extensive adhesions should be burned through at a point as far away from the lung as possible. From the author's experience in 150 cases he says that cordlike adhesion up to the thickness of the little finger can always be severed without much danger; that the same is generally true of membraneous adhesions. Great care must be used, however, in the severance of large flat adhesions and it is best here only to burn through the granulation tissue which attaches the lung to the chest wall. In many such cases complete severance can be accomplished only by means of several successive operations. The operation is associated with certain complications most of which are, however, not serious. Subcutaneous emphysema is very frequent about the site of puncture. This lasts only two or three days and produces no ill effects. The operation is followed by pleural exudation in a considerable proportion of cases, some of which go on to the development of empyema. The majority of the exudates, however, are rather small and are usually absorbed within one to two weeks. In his series, he was able to complete the operation in a technically satisfactory manner in 121 out of the total 150 cases. Of these, the results were clinically satisfactory in 99. The most satisfactory clinical results are obtained in patients having cordlike and membranous adhesions located laterally. The next most satisfactory group is that with similar adhesions about the apex. Other forms and locations give results of somewhat doubtful value.

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**The Significance of the Liver Diet in Pernicious Anemia.**—ARON (*Med. Klin.*, 1928, **24**, 1696) directs attention to the fact that certain of the very severe anemias of childhood, such as the normoblastic anemia of von Jaksch, are nearly identical in many of their characteristics with pernicious anemia of the adult. He emphasizes the fact long known to pediatrists that these forms of anemia can be cured only

by dietetic methods. The effective diets are limited to those especially selected for their extreme richness in vitamin content, thus indicating that these forms of anemia probably rest upon a basis of vitamin deficiency. Intermediate between the juvenile anemias and pernicious anemia is the condition of tropical sprue in which the anemia resembles closely both the juvenile and the adult pernicious types and to which there is also added a group of symptoms somewhat analogous to those found in scurvy. This condition is also responsive only to the use of vitamin-rich diets. The author points out further the fact that the mammalian liver constitutes the chief reservoir for the storage and for the gradual release to the body of all three of the important vitamins. The liver is, in fact, more richly supplied with vitamins than any other food substance known. On the basis of this fact and of the analogies between the infantile anemia and sprue on the one hand and pernicious anemia on the other, the author suggests that the reason for the extraordinary therapeutic activity of liver and liver extracts in pernicious anemia is due to its high content of vitamins. He suggests that the highly specific value of liver and liver extract in pernicious anemia establishes this disease also among those due to vitamin deficiency. The failure of other methods of dietotherpy to relieve pernicious anemia anemia is, in his opinion, due largely to the difficulty of introducing a sufficient quantity of the necessary vitamins in the form of the usual foodstuffs owing to their great bulk. It has been shown already that it is necessary to feed large quantities of the extraordinarily rich liver in order to control the disease. It seems probable, therefore, that once the disease is established its cure can be brought about only by the use of extremely large quantities of vitamins, such as has been proved to be the case with the juvenile anemias and with sprue. The suggestion is further made that by the administration of approximately equal amounts of the vitamins A, B and C, as obtained from other sources than liver, one should also be able to cure pernicious anemia. Up to the present time, however, no thoroughly adequate experiments have been made along these lines. The need in all of these forms of anemia for the administration of very large quantities of vitamins suggests that they are associated with: (1) Impaired absorption or increased destruction of the vitamins in the intestinal tract; (2) increased vitamin consumption due to infection; or (3) increased vitamin need through disturbances in the activity of internal secretions.

Contrasting sharply with the foregoing viewpoints is that of Ponticaccia and Campanacci (*Klin. Wchnschr.*, 1928, **7**, 2153), who contend on the basis of their personal observations that the chief action manifested by liver, by which it brings about the rapid control of pernicious anemia, is due to its capacity to check the hemolytic destruction of the red cells. In their opinion this prompt antihemolytic action accounts for the immediate improvement in the general condition of patients with pernicious anemia which occurs before there are any evidences of change in the blood picture. Their contention seems further established by the prompt diminution in the content of bilirubin in both blood and urine and by the rapid increase in the cholesterin content of the blood to supernormal levels. They believe that the changes in the bone marrow characteristic of pernicious anemia are not of fundamental importance, but are strictly secondary to disturbances in its function which follow as a result of pronounced hemolysis.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

**The Treatment of Rickets with Irradiated Ergosterol.**—WILKES, FOLLETT and MARPLES (*Am. J. Dis. Child.*, 1929, **37**, 483) treated 24 infants with rickets varying from mild to severe with irradiated ergosterol. Two babies with tetany were cured by the use of irradiated ergosterol. The irradiated ergosterol is in the form of a commercial preparation and was well taken and well tolerated. Two of the patients to whom it was given had severe bronchopneumonia and in several others cod-liver oil administration had been attempted but it had been refused or vomited. In their observations, they confirm the reports of other authors who had used irradiated ergosterol. They found that this preparation requires about three weeks to cause serum blood phosphorus and calcium concentration to return to normal. They also found that it required about the same time for the Roentgen ray signs of the healing of the rickets to appear and it further required about six weeks to obtain complete healing. These averages compare favorably with those obtained from the use of cod-liver oil, quartz light and eggs. Craniotabes was healed within an average period of one month in a series of 12 patients. Healing of the rachitic bone took place in one patient who had bronchopneumonia in spite of a low serum phosphorus and a calcium product of 20.5 mg. per 100 cc. They caution against using irradiated ergosterol in patients with tetany who show a high blood-phosphorus content. They believe that irradiated ergosterol is not a perfect preventative to rickets. They observed craniotabes developing in one patient who had received prophylactic doses of irradiated ergosterol although this lesion healed promptly when the irradiated ergosterol was continued in unchanged amounts.

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**Intraperitoneal Blood Transfusion.**—COLE and MONTGOMERY (*Am. J. Dis. Child.*, 1929, **37**, 497) claim that satisfactory therapeutic result is obtained by the intraperitoneal method as could be expected by the intravenous. In their 237 transfusions in 117 patients, reactions occurred in less than 7 per cent of the cases and in only 2 or 3 instances were they of noticeable importance. These reactions usually consisted of restlessness and of abdominal discomfort but were rarely accompanied by fever. Properly citrating the blood prevents these reactions. As these transfusions were all performed in private practice in nearly every case, the parents were the judges of the reactions which is fairly good evidence that they were slight. It is certain that the marked reactions which are rather commonly seen in the intravenous method occur much less often after intraperitoneal transfusions. In their entire series there were no evidence of injury to any abdominal organ nor have they ever experienced anything which could be regarded in any way as an unfavorable effect for the intraperitoneal injection. Of their series 20 patients

died and 3 came to autopsy. In one case some unabsorbed blood was found in the abdominal cavity but this patient was dying when the transfusion was given. The small amount of disturbance to the patient from the intraperitoneal transfusion is worthy of consideration. The struggling and crying incident to intravenous transfusion is often very harmful. The contraindications for intraperitoneal transfusion are the same as for any other type of transfusion with the addition that it should never be used where there is any question of intraäbdominal disease or where even temporary abdominal discomfort might be a disadvantage, such as in severe cardiac disease or acute pneumonia. The use of citrated blood intraperitoneally has little use in the rapid replacement of blood volume in shock or hemorrhage and the hemostatic effect is probably delayed. In every other respect it possesses all of the advantages of intravenous transfusion with reduced reaction and easy administration.

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**An Experimental Study of the Use of Unsweetened Evaporated Milk for the Preparation of Infant Formulæ.**—MARRIOTT and SCHOENTHAL (*Arch. Pediat.*, 1929, **46**, 135) discuss the suitability of unsweetened evaporated milk in the preparation of infant-feeding formulæ. This product was fed to 752 young infants. A series of 670 infants either breast fed or fed on other milk modifications was used as a comparison. In the series fed on evaporated milk there were 570 newborn babies, 107 young infants in dispensary and private practice and 75 infants ill in hospitals. Eleven infants were premature. It was found that a larger percentage of the newborn babies regained the birth weight by the end of fourteen days when on formulæ prepared from evaporated milk than those fed exclusively on the breast or given other supplementary formulæ. The average daily gain in weight of the babies fed on formulæ prepared from evaporated milk was exactly equal to that of babies fed exclusively on breast milk or on formulæ prepared from bottled pasteurized milk. A group of sick infants made an average daily gain on evaporated milk formulæ which was somewhat better than that of a group of control infants fed by other methods who were also in a hospital during a period of observation. It was observed that the premature infants made especially good gains when fed on evaporated milk. As the result of their observations the authors feel that unsweetened evaporated milk from the nutritional standpoint is the full equivalent of pasteurized or boiled whole cows' milk. The continued use of evaporated milk as routine food for normal babies is not attended by nutritional disorders. It was found to be especially suitable for premature babies. It was found that evaporated milk when suitably modified was a satisfactory food for sick infants especially those suffering from nutritional or gastrointestinal disorders. The distinct advantages which recommend evaporated milk for general use are its sterility, its ready digestibility and its uniformity of composition.

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**The Early Diagnosis of Pertussis.**—ORGEL (*Arch. Pediat.*, 1929, **46**, 149) made observations on the intradermal reactions using several different pertussis vaccines. Using a vaccine containing 3000 million bacilli per cc. he obtained positive intradermal reactions 81 per cent of all the children tested and he found that the percentage of reactions

increased with the concentration of the vaccine. Using a vaccine containing 2000 million bacilli per cc. he obtained reactions in 50 per cent of all children but in 80 per cent of those children having pertussis and in 49 per cent of children that had previously had pertussis. Pertussis vaccines in concentrations less than 2000 million bacilli per cc. rarely caused positive intradermal reaction regardless of whether or not the child was suffering with pertussis. Other vaccines if containing 2000 million or more organisms per cubic centimeter cause positive intradermal skin reactions. Aolan did not cause any reactions in the children tested in this series. Colon bacillus vaccines in a dilution as low as 400 million bacilli per cc. gave positive intradermal reactions in all the cases tested. The author feels that a positive intradermal skin reaction obtained by the use of bacillus pertussis vaccine containing 2000 million bacilli per cc. is not diagnostic of pertussis.

**The Leukocyte Count in Epilepsy.**—Patterson and Weingrow (*Arch. Neurol. and Psychiat.*, 1929, **21**, 412) in studying 182 cases of epilepsy found 50 per cent showing an increase over the normal in the total white cell count, while in 20 per cent the count fell below normal. The leukocytosis which they observed was not neutrophilic but lymphocytic. Different evidences of epileptic leukocytosis being influenced by digestion of food was not observed. Within the limits of physiologic variation, the rise in the leukocyte count is the same in nonidiopathic as in idiopathic epilepsy. It seems that the leukocytosis frequently met in epilepsy is not due to the disease itself but to some associated phenomena. A connection between the leukocyte count in epilepsy and the presence or absence of an aura apparently does not exist. No relationship could be shown between onset and duration and the white cell count nor does the leukocyte count in epilepsy seem to be affected by the secondary anemia which often accompanies the disease.

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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**Lipid Studies in Xanthoma.**—Wile, Eckstein and Cutis (*Arch. Dermat. and Syphilol.*, 1929, **19**, 35) find that xanthoma, long considered to be a cholesterol-containing tumor of the skin, contains in reality very little cholesterol, and considerable amounts of other lipids. In several cases a rapid clinical response with involution of the tumors was produced by placing the patients on a reduction diet, as for obesity.

The authors believe that the cholesteremia usually observed in these patients and the formation of the lipid tumors are both expressions of an underlying disturbance of fat metabolism, possibly of central origin.

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**Hemotogenous Production of Dermatomycoses.**—FRIED and SEGAL (*Arch. Dermatol. and Syphilol.*, 1929, **19**, 98) find that in confirmation of the results of Saeves, intravenously injected suspensions of Trichophyton organisms localize in the skin of animals only if there has been a certain degree of capillary injury such as is produced by shaving. The trauma to the vessels permits the fungus in the circulation to "leak through," producing lesions only in the skin. The intravenously introduced parasite circulates in the blood for not less than three days.

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**Experimental Urticaria Factitia.**—WALZER, *Arch. Dermatol. and Syph.*, 1928, **18**, 868) found that injection of the serum of dermographic subjects into the skins of normal persons did not transmit to the normals the capacity for developing wheals on trauma to the injected sites, except in the case of the serum of a single patient, with a papular dermatosis which the author was unable to diagnose, but which apparently had an urticarial phase. Following the injection of this patient's serum into their skins, 7 of 12 normal subjects reacted to stroke or other mechanical trauma at the site of injection with the production of wheals. The author is convinced that the transferred substance which brings about wheal formation in normal subjects, is not histamin as described by Lewis. In the discussion it was suggested that the substance might be tyramin, recently recognized in the circulation of some subjects.

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**The Elimination of Bismuth from the Human Organism.**—ENGELHARDT (*Arch. f. Dermatol. u. Syphilol.*, 1928, **156**, 1). This is a 40-page summary of studies of the elimination of bismuth as tested with several types of preparations, by oral, inunction, intravenous and soluble and insoluble intramuscular injections in aqueous and oily suspensions. Only the principles which have therapeutic application are here cited. A slight but unimportant elimination of bismuth follows administration by mouth and inunction. The elimination is rapid following intravenous injection. This fact, together with the necessarily more frequent injection, the great toxicity, and the needlessness of excessively rapid bismuth effect as a spirillicide when the arsphenamins are available, leads the author to deprecate intravenous use. The elimination of bismuth after injections of an oil suspension occurs at an unpredictable and variable rate, bearing some relation to eccentricities of absorption. The best eliminated products are the vegetable oil suspensions of iodin and quinine-containing bismuth salts. The author approves the use of massive doses of an insoluble bismuth salt at the outset of a course, not because of any immediate massive effect, as had been proposed, but because in this way the slow absorption is to some extent compensated for. Subsequent doses must be reduced. The author considers that where arsphenamin is used coincidently there is no occasion for massive dosage or for intravenously administered bismuth. The most uniform absorption is secured with water-soluble bismuth compounds but these are by far the most painful and their limited depot-forming

value is also a drawback. Colloidal bismuth preparations are of value in the milder types of combined bismuth therapy. The daily dose of metallic bismuth by whatever salt introduced, should not in general exceed 25 to 30 mg. The average course should be about 1100 to 1300 mg. metallic bismuth in a vegetable oil suspension. The interval between courses with a water-soluble or colloidal preparation should not exceed six weeks, and with the intramuscular use of an oil-suspended salt in amounts of 1000 mg. metallic bismuth and over, the interval should not be less than eight to ten weeks.

**The Treatment of Epidermophytosis.**—CASTELLANI (*Lancet*, 1928, ii, 595) discusses a new treatment in certain types of ringworm infections, mainly those caused by Epidermophyton inguinale and E. rubrum. He recommends the employment of a fuchsin paint prepared by adding to the ordinary laboratory basic carbol fuchsin stain 1 per cent boric acid, 5 per cent acetone and 10 per cent resorcin. This may be applied in full strength as often as twice daily. The writer catalogues the variety of cases in which this treatment is unusually valuable, namely: (1) ringworm of the feet and toes particularly with secondary pyogenic infection; (2) cases of epidermophytosis simulating moist eczema; (3) epidermophytic pompholyx; (4) myocotic pruritus of the anus and vulva. In ordinary ringworm of the body and groin the use of Whitfield's ointment appears preferable.

**Liver Diet in Acne Vulgaris and in Furunculosis.** — SUTTON (*Arch. Dermat. and Syph.*, 1928, **18**, 887) treated 27 cases of acne vulgaris and furunculosis with a diet high in liver. He employed both the fresh and the powdered extract. The quantity of extract ranged from 24 to 72 doses over an average period of twelve days. The best clinical response was obtained in the patients with pale moist flabby skins who presented deep-seated lesions of the indolent type.

**Some Remarks on the Bactericidal Properties of Zinc Oxid.** HAXTHAUSEN (*Brit. J. Dermat. and Syph.*, 1928, **40**, 497) believes that in addition to the known properties of drying, protection, and binding of irritants, zinc oxid possesses bactericidal qualities that enhance its value in cutaneous conditions. The author noticed that while talcum and kaolin had no effect on the growth of staphylococci, strewing zinc oxid over the surface of a Petri-dish containing agar inoculated with staphylococci caused small but distinct sterile zones about each deposit of zinc oxid. No effect was noted in the case of Bacillus pyocyaneus, but slight effects on Bacillus coli. However, the resistant Bacillus subtilis showed a distinct sterile zone. Most noticeable were the zones for staphylococci and streptococci particularly when the pH of the medium was reduced from 7.5 to 5.5. Commercial zinc oxid was found to exhibit a stronger action than the chemically pure drug. The action on bacteria appears to be due to the development of acid by the strain of organism, the consequent partial dissolution of the chemical, and the formation of a compound that can give off free zinc ions. The author concludes that there is every reason to believe that a similar bactericidal process takes place *in vivo* when zinc oxid is applied as an ointment to the skin, and the action is especially pronounced where staphylococci and streptococci are involved.

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Early Clinical Diagnosis of Cervical Cancer.**—The early clinical diagnosis of carcinomatous material is often a very difficult matter. Of course a section of tissue can be examined under the microscope and a diagnosis readily made in most cases, but where the case is being considered from the standpoint of operability, this type of diagnosis is of little aid in determining just where the malignant epithelium ends and the normal cells begin. In the case of the cervix, even if a section were made from the border of the growth, this would only show the conditions at that particular point and would give no information relative to the extent throughout the remainder of the circumference of the cervix. In their clinic in Vienna, according to SCHILLER (*Zentralbl. f. Gynäk.*, 1928, **52**, 1886), considerable work has been done with vital staining of the tissues as a means of differentiating malignant from benign cells. It was found to be of little value because all living cells took the stain deeply whether they were carcinomatous or normal, while only necrotic cells failed to take the stain. On the other hand, it was found that when Lugol's solution was applied to the cervical and vaginal epithelium the normal cells were stained a deep dark-brown color in a few seconds, whereas pathologic cells were not discolored. This differentiation is supposed to be due to the difference in glycogen content in normal and in carcinomatous cells. The test is considered specific only in that what becomes discolored is normal epithelium. Lack of staining does not necessarily mean that the tissue is carcinomatous, although it usually is, but it may be due to hyperkeratotic epithelium which is frequently seen associated with uterine prolapse. Such epithelium contains only a very small amount of glycogen and therefore does not become stained upon the application of an iodin solution.

**Operation Versus Irradiation in Cervical Cancer.**—These gynecologists who still prefer operation to irradiation in the treatment of cancer of the cervix are few and far between, especially in this country. In Europe, however, there seem to be several clinics in which the radical operation is still performed with a fair amount of frequency. In comparing the relative value of hysterectomy and irradiation, FORGUE (*Am. J. Surg.*, 1928, **5**, 44), of France, states that when dealing with a beginning case which appears definitely operable from both the technical point of view (mobile uterus and flexible vaginal fornices) and the clinical point of view (no contraindication in the state of the patient)

he believes that panhysterectomy offers advantages which compensate for the operative risk. It is logical to employ preparatory radium treatment before the hysterectomy and it carries an additional factor of safety in that it sterilizes the cervicovaginal passages, but in these favorable cases he believes that one can and should remain in the domain of surgery alone. In practice, this supplementary preoperative radium therapy presents one of two difficulties, namely, the patient who has submitted to treatment by irradiation will have a tendency to be content with this treatment on account of the amelioration of symptoms, and if the patient be a private case she may refuse to pay the expense of both radium therapy and surgery. He states that his opinion is only provisional and may be modified by improved radium technique with correspondingly improved results.

## OPHTHALMOLOGY

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**On Nonhypophyseal Affections of the Chiasma.**—HENNING RONNE (*Acta Ophthalmologica*, 1928, **6**, 332–343) refers to the crossing of the macular fibers in the posterior chiasma angle and points out that in hypophyseal affection developing in the meridian behind the chiasma there macular fibers will be first involved. The clinical consequence of this is development of a bitemporal hemianopic central scotoma. These small defects in the field of vision are not noticed by the patient and may be overlooked. "The site of the macular fibers in the posterior chiasma angle is, also in another respect, of diagnostic significance, namely, in differential diagnosis between tractus-hemianopia and hemispheric hemianopia. Hemianopia originating from the optic tract is frequently due to tumorous formation, and the tract being of relatively short extension, the pressure will, in the majority of cases, reach the proximal chiasma angle; at this juncture the macular fibers will be involved, the result being reduction of central vision in one or both eyes. Reduction of visual acuity is, therefore, the best diagnostic criterion in differentiating between tractus hemianopia and hemispheric hemianopia, for in the latter form of hemianopia visual acuity is always normal." The various affections which, according to the author's experience, develop in the chiasmal region are tumorous formation within the chiasm itself, primary neuritis within the chiasm, optic nerve atrophy seen in tabes dorsalis (of which the author has observed 4 cases) and multiple sclerosis. Frontal lobe tumor may also give direct compression symptoms in the chiasma in a manner similar to hypophyseal tumor resulting in an irregular hemianopic visual field.

**Ocular Tuberculosis and Constitution.**— GRONHOLM, V. (*Acta Ophthalmologia*, 1928, **6**, 297–309) refers to intra-ocular tuberculosis alone,

including chronic tuberculous uveitis, scleritis, and keratitis and the affections which arise in sequel to these. The etiology of these conditions can but rarely be verified by bacteriologic or inoculation test. The evidence of ocular tuberculosis at the Helsingfors University Eye-Clinic amounted to about 0.3 per cent. The age distribution of 100 cases of ocular tuberculosis was as follows— 66 per cent became manifest in the ages between fifteen and thirty years and most frequently between twenty-one and twenty-five years, while the disease was of comparatively rare occurrence before puberty and after the thirtieth year of age. The mean age of incidence for ocular tuberculosis is in the twenty-third year in either sex. The proportion of males to females affected were 1 to 3. Pulmonary tuberculosis could be demonstrated in only 18 of the cases, being found twice as often in men as in women. Affection of the cervical or bronchial glands, or of both, was of frequent coincidence with ocular tuberculosis, being demonstrated in 55 of the 100 cases. His observations indicated that ocular tuberculosis attacks apparently healthy individuals with an abated or fairly benign tuberculosis of some other organ, most frequently in the lymphatic vascular system, rarely in the lungs.

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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**A Comparative Study of Chronic Sinusitis with End Results Following Intranasal Operations.**—In presenting his observations on a group of cases limited to: (1) Chronic suppurative sinusitis; (2) chronic hyperplastic ethmoiditis; (3) polypoid degeneration of the mucosa, and excluding those instances of chronic empyema involving only the maxillary sinus, REAVES (*Arch. Otolaryngol.*, 1929, **9**, 23) emphasizes the difficulties of diagnosis and dwells upon the relative merits of the various methods of examination, including history, nasopharyngoscopy, transillumination, radiography and visual acuity tests. After a consideration of the symptomatology, the author, in treating of the etiology, discusses infection as the cause of chronic suppurative sinusitis; the rôle of exogenous irritants, low-grade infection, endogenous toxins and metabolic disturbances in the chronic hyperplastic forms of ethmoiditis: and the allergic and infectious phases of polypoid degeneration. Following a detailed description of his intranasal operative technique, his results from surgical intervention are tabulated. It was found that of the total number of operations performed, including 57 for chronic suppuration, 54 for chronic hyperplasia and 39 for polypoid degeneration, 1.3 per cent of cases were not improved, 10.6 per cent were unsatisfactory and 85.2 per cent were satisfactory. In concluding, Reaves calls attention to a definite pathologic condition of the nasal mucosa with a tendency to formation of polypi and rarefaction of bone and a fairly constant group of symptoms. This condition differs from true

hyperplasia by the absence of thickened bone and headache. He further states that the degree of headache associated with chronic suppuration depends on the condition of the bone; and that most cases of chronic sinusitis will clear up after ventilation and drainage have been established.

**The Incidence of Nasal Sinusitis with Diseases of the Ear.**—"Though the problems of deafness in the adult are better understood, prevention and treatment are less effective than in children. If progressive deafness is to be mastered, the periods of its inception and pre-inception will furnish the most promising grounds for research. Any deafness may become progressive in some degree, and it is not yet known when or why any deafness may presage permanent or progressive deafness. For these reasons, a study of the ears of children is desirable, and any correlation that may be established between the disease of the ear and factors heretofore thought incidental should be of some value." As it is recognized that an intimate relation between the ears and the nose and nasopharynx exists, FOWLER (*Arch. Otolaryngol.*, 1929, **9**, 159) by charts, tables and discussion, presents the results of an exhaustive investigation relative to the incidence of paranasal sinusitis and aural disease occurring in 100 consecutive cases in children. From his analysis of those observations, the author summarizes that complete histories, tests and stereoroentgenograms give invaluable data for the study and treatment of otologic lesions; that 57 per cent of the cases showed moderate or severe involvement of the nasal sinus spaces; that 71 per cent exhibited pathologic changes in the ethmoid septa; that 86 per cent revealed pathologic processes in the sinuses; that the chronicity of the suppuration in the ear was directly proportional to the involvement of the sinus spaces, and indirectly proportional to that in the ethmoidal septa; that diseases of the nasal sinuses, and of the sinuses of the ear, were intimately associated, and prevention, alleviation and cure of one necessitates the prevention, alleviation and cure of the other; that in virtually all of the children there had been inflammation not only of the ears, but also of the nasal sinuses; and that the coëxistence of otitis and active or latent sinus infection is not coincidental.

**Inflammatory Affections of the Orbit of Nasal Origin.**—DAVIS (*J. Laryngol. and Otol.*, 1929, **44**, 164) found that the commonest cause of orbital inflammation of nasal origin was suppuration of the frontal sinus in adults (16 cases) and ethmoidal suppuration in children (7 cases). In no instance was the orbital involvement due to extension of the infection from the maxillary or sphenoidal sinuses. Frontal sinus suppuration when it involves the orbit produces a characteristic downward and outward displacement of the eyeball, whereas ethmoidal suppuration displaces the eyeball outward and forward. Diagnosis is made on intranasal examination, radiography and differentiation from cysts, mucocele and neoplasm. The treatment depends on the source of infection and the presence or absence of an orbital abscess. If an abscess is present, immediate incision and drainage of both the abscess and the affected sinus is indicated. If the orbital inflammation is non-suppurative, drainage of the affected sinus usually suffices. Occasional complications are cavernous sinus thrombosis and secondary optic atrophy.

# RADIOLOGY

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**Diathermy in Pneumonia.**—Reports from all parts of the country and from abroad show a steady increase in the use of diathermy in pneumonia, according to STEWART (*Arch. Phys. Ther., Roentg. Ray, Radium*, 1928, **9**, 437). After six years experience Stewart makes a definite claim for a lessened mortality in treated cases. In the average case he advises treatment every four hours, except during the early morning, with electrodes sufficiently large to cover the involved area, anteriorly and posteriorly, at 1400 to 1800 ma. At first caution was advised in cases complicated with empyema, but now Stewart not only continues but intensifies the treatment, once the patient has passed the critical stage of his pneumonia.

**Ultraviolet Irradiation in Skin Diseases.**—NORRIS (*Arch. Phys. Ther., Roentgen Ray, Radium*, 1928, **9**, 448) remarks sarcastically that ultraviolet rays have achieved a remarkable vogue and are being applied indiscriminately for an imposing list of conditions ranging from flat feet to shinning scalps. Norris has tried it without favorable consequences is ichthyosis, common warts, vililigo, epidermolysis bullosa and certain other conditions. However, in psoriasis, eczema, particularly acute and weeping types, if there is not much infiltration, and in acne vulgaris, varicose ulcers with associated dermatitis, nevi, and lichen planus, Norris finds it very useful. It is of value in certain cases of generalized pruritus, and in several instances of chronic urticaria Norris has given the major credit to ultraviolet irradiation, universally applied, for perfect recoveries. In ivy poisoning and generalized arsenical dermatitis it has reduced pruritus, dried the areas, and promoted recovery. It has produced gratifying results in impetigo contagiosa, likewise in erythema multiforme. Norris goes on to state emphatically that in certain skin conditions ultraviolet rays are distinctly harmful, as, for example, in such diseases as xeroderma pigmentosum. Technique of applying the irradiation is a matter of importance and requires training and experience.

**Roentgenologic Study of the Abdominal Viscera.**—MOODY and VAN NUYS (*Am. J. Roent. and Rad. Ther.*, 1928, **20**) have carried out a study of abdominal viscera, especially the liver and spleen, by simple roentgenography. They find that long livers having their lower tip in the pelvic cavity as much as 5 cm. below the interiliac line are normal. More men than women have long livers. The lower border of the spleen

is most commonly found opposite the upper half of the third lumbar vertebræ, but long spleens with their lower border opposite the fourth lumbar vertebra are not uncommon, especially in men, and without any history of malaria. There is some evidence that exercise decreases the spleen in man, and that loss of blood given for transfusion has the same effect.

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**Extra-abdominal Affections Giving Gastrointestinal Symptoms, with Special Reference to the Ménière Syndrome.**—With evident approval, CRANE (*Radiology*, 1928, 11, 447) quotes W. J. Mayo as follows: "The stomach is the alarm box of the abdomen, and the hose is often turned on the alarm box instead of the real conflagration." This, says Crane, is one reason why cases of abdominal angina, the visceral crises of the erythemas, mucous colitis and Ménière's disease continue to be operated on for supposed appendicitis, ulcer or gall stones. No one of these is common but in the aggregate they assume considerable clinical importance. For many years Crane has been impressed with the frequency with which cases of Ménière's disease come in for examination of the gastrointestinal tract. Even physicians themselves when suffering from this condition rarely exercise the personal detachment necessary to disregard the call of the digestive tract.

To suggest an adequate reason for negative roentgenologic findings may be a defense reaction on the part of the roentgenologist. If he has not found the trouble it is because he does not know how—that is the attitude of some patients and occasionally of some surgeons. Negative Roentgen ray findings may be the outcome of some of the finest work in roentgenology, and yet a patient may sum up the whole, painstaking investigation with contemptuous brevity in: "Oh, they found nothing." Study negative findings: it is in this field that future Roentgen ray discovery may be expected. Behind every negative finding at apparent variance with the symptoms lies a worth-while diagnostic problem. If the roentgenologist will but exercise his training in the general diagnosis of internal disease, he will acquire increased precision and will less often be lured by the mirage so perfectly illustrated in Ménière's syndrome.

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**Cholecystography and Transduodenal Drainage.**—In an extensive series of cases SNOW (*Am. J. Roent. and Rad. Ther.*, 1928, **20**, 358) found that more than 90 per cent that had both duodenal drainage and the Graham test, gave similar results in indicating a normal or abnormal condition. A gall bladder which responds normally both to the Graham test and duodenal drainage is usually normal at operation. Failure to obtain B bile by the drainage test usually means failure to visualize the gall bladder with dye and the viscus is usually found at operation to be diseased. Gall bladders containing stones usually yield pathologic bile by the drainage test and often no B bile. A gall bladder which is faintly visible before and after dye and does not empty after fatty food, is definitely abnormal; in this series a hydrops was found in such cases and the drainage test yielded no B bile.

# PATHOLOGY AND BACTERIOLOGY

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**Focal Necrosis of Liver.**—Various explanations have been offered to account for the irregular localization of focal necroses of the liver in the infectious diseases. The action of toxic substances and the presence of vascular thrombi have usually been indicated as the cause of these liver lesions. EDINGTON (*J. Path. and Bacteriol.*, 1929, **32**, 1) encountered an endemic among guinea pigs due to Bacillus ærtrycke. In studying the organs from the fatal cases he observed the frequent presence of focal necrosis in the liver. He was unable to determine the presence of vascular thrombi, and the cellular infiltration by large monocytes was secondary to the process of necrosis. He was unable to find a direct relation between the lesions and localized aggregations of bacteria. Subsequently, he undertook an experimental study to determine whether bile stagnation was in any way related to the focal dissemination of the necrosis. Guinea pigs were operated upon, the common bile duct ligated, and then given a subcutaneous inoculation with Bacillus ærtrycke. These animals showed focal necroses within eighteen hours after the inoculation. Animals which alone were given ærtrycke and killed within twenty-four hours showed no focal necroses. Likewise animals in which the bile duct was ligated but not inoculated showed no necroses. The author was able to produce similar lesions by the use of Bacillus enteritidis, streptococci, and Bacillus diphtheriæ or its toxin, in place of the Bacillus ærtrycke. The author believes that the toxins from these organisms produce a cloudy swelling of the liver cells which interferes with the proper escape of bile. This retention of bile assists in further damaging cells that have been rendered unstable by the bacterial poisoning.

**Diffuse and Nodular Fibrosis of Adventitia of Aorta (Rheumatic Periaortitis).**—BARNARD (*J. Path. and Bacteriol.*, 1929, **32**, 95) studied a single case of rheumatic aortitis arising in a young man, aged twenty-three years, who gave a history of recurrent attacks of rheumatic fever. The fatal illness was related to cardiac failure associated with a chronic endocarditis of the mitral and aortic valves. The aorta showed fibrous thickening in its thoracic portion. The fibrosis varied from nodular thickenings both in the intima and adventitia to the diffuse connective-tissue hyperplasia extending over the larger part of the vessel. This fibrosis also extended along some branches of the abdominal aorta. The microscopic analysis failed to reveal recent cellular infiltration, but showed an increase in the connective tissues on the outer side of the aorta

and to some extent entering the middle coat. The author points out that a differential diagnosis between syphilis, periaortitis nodosa, and rheumatic lesions must be made. The absence of any other lesions of a syphilitic nature, and the lack of aortic changes as found in syphilis rules out this condition. Likewise there was no evidence of periarotitis nodosa on any arteries of the peripheral system. He finds that the lesions which he described were similar to those described by Klotz in 1912, where it was shown that localized and diffuse fibroses upon the aortic wall are the outcome of rheumatic inflammatory processes in which their early stage was accompanied by a nonsuppurative cellular response.

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**Chronic Peptic Ulcer of the Esophagus.**—The esophagus may occasionally suffer ulceration similar to the lesions which are found in the stomach and duodenum. The esophageal ulceration, however, is very rare, STEWART and HARTFALL (*J. Path. and Bacteriol.*, 1929, **32**, 9) stating that only a single case had been encountered in over 10,000 autopsies performed during the last eighteen years. However, others give a higher incidence, some amounting to 1 in 200 cases. The peptic ulcer arises in the lower portion of the esophagus, usually at the border of the cardiac orifice. The ulcer is prone to be chronic, showing a fibrosis in the floor and accompanied by little or no inflammatory exudate. The process of necrosis may extend through the walls of the esophagus, leading to perforation. In a few instances the development of carcinoma at the edge of the ulcer has been described. The authors report the case which they observed at autopsy arising in a man, aged fifty-three years, who gave a history of digestive disturbance with an occasional vomiting of blood. At autopsy the ulcer was found to be of large size, showing a perforation just above the level of the cardia. This perforation passed through a dense mass of fibrosis and entered the right pleural cavity. It was interesting that the authors found the presence of two large patches of gastric mucosa in the upper esophagus just below the level of the cricoid cartilage. Although misplacements of the gastric mucosa are not uncommon in the esophagus, the question arises whether these anomalies are associated with the development of the chronic ulcer.

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**Pathogenesis of Intestinal Amebiasis in Kittens.**—REES (*Arch. Path.*, 1929, **7**, 1) has undertaken to study the early stages of the intestinal lesions arising in experimental amebic dysentery. He introduced a new method for infecting the animals with E. histolytica grown upon cultures. In place of the usual procedure of infecting the animals by means of a rectal tube, the author, by means of a laparotomy ligated the lower portion of the rectum and injected the cultures directly into the bowel. The author found that lesions appeared forty hours after the operation, and became quite severe after ninety hours. Widespread destruction of mucosa took place, and it appeared as if the effect of the injected amebæ was directly upon the surface membranes and not by the development of small ulcers in the crypts of the glands. The first lesions were in the vicinity of the ileocecal valve, and when ulceration occurred the submucosa did not appear to be invaded beyond that of the mucosa. The injury results from the presence of a cytolytic toxin.

# HYGIENE AND PUBLIC HEALTH

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**The Problem of Automobile Exhaust Gas in Streets and Repair Shops of Large Cities.**—BLOOMFIELD and ISBELL (*Pub. Health Repts.*, 1928, **43**, 750) conducted an extensive field and laboratory study, which is best given in their own summary: This survey was undertaken to ascertain whether or not a health hazard from carbon monoxid existed in the streets of our large cities, inside of autobusses and in repair shops. Fourteen of the largest cities in the country were visited, having a combined population of over 19,000,000 and 250 samples of air were obtained for carbon-monoxid analysis. These samples were analyzed by the iodin-pentoxid method, using a liquid-air cooling tube, which was shown to be necessary in order to eliminate gasoline vapor, a substance which tends to vitiate the results of the analysis. Our street samples were taken in such a manner as to approach the most congested conditions that may exist at a busy traffic intersection. Hence, it is felt that these results indicate the maximum hazard from automobile exhaust gas that may exist today in our metropolitan thoroughfares. The average of 141 tests made in city streets at peak hours of traffic showed a contamination of 0.8 part of carbon monoxid per 10,000 parts of air. Only 24 per cent of all the street samples had more than 1 part of carbon monoxid in 10,000 of air, and in only one location, a covered passageway, was there as much as 2 parts per 10,000. Samples taken inside of autobusses yielded even lower concentrations of carbon-monoxid gas. The figures for street air, when viewed in the light of present-day standards of exposure to carbon monoxid, do not reveal the existence of a health hazard from this source in our city streets. The only individual who may possibly be exposed to a health hazard from inhaling street air containing automobile exhaust gas is the traffic officer. This potential hazard may be minimized by diminishing the duration of exposure at the most congested traffic stations. Of the 102 tests made in 27 garages in the 14 cities visited the average carbon-monoxid content was found to be 2.1 parts in 10,000. More than half of the samples (59 per cent) contained over 1 part of carbon monoxid, and 18 per cent of all the samples contained over 4 parts of this gas in 10,000 parts of air. These results for repair shops show a dangerous condition that demands the serious consideration of those concerned. This hazard in repair shops may be reduced to a minimum by not allowing the motors of automo-

biles to run longer than thirty seconds unless the car is in necessary motion or the exhaust is connected to the outside air by a direct air-tight outlet of ample caliber. Without such outlet no automobile engine should be allowed to run indoors, except to reach its berth or to leave by the shortest route. All of these samples were taken in garages of considerable size. The great danger to life is unquestionably in the small private garage containing one or two cars. Under any circumstances the discharge of an automobile exhaust into a roofed inclosure should be regarded as a hazardous act.

**A Further Study of Experimental Black Tongue with Special Reference to the Black Tongue Preventive in Yeast.**—GOLDBERGER, WHEELER, LILLIE and ROGERS (*Pub. Health Repts.*, 1928, **43**, 657) on the treatment of black tongue in dogs is covered by the following summary and conclusions: The black-tongue-producing potency of a basic experimental diet and of three modifications was tested 33 times in 31 dogs with the production of 33 separate attacks of black tongue. Only 1 of these attacks developed at the end of a period longer than sixty-one days. Experimental black tongue is due to a dietary deficiency which is capable of being corrected by something contained in yeast. This something, or black-tongue preventive, in yeast is inactivated or destroyed by heat sufficient to char the yeast; retains its preventive potency in large measure, if not entirely, after heating in the steam autoclave at a pressure of 15 pounds for seven and a half hours; is adsorbed from an acidulated aqueous extract of either dried yeast or of yeast first autoclaved at a pressure of 15 pounds for two and a half hours by English fuller's earth. It cannot be identified with any of the older well-recognized dietary essentials, but is believed to be identical with the thermostable substance of Smith and Hendrick. The black-tongue preventive and the pellagra preventive are both present in yeast. Taken in conjunction with certain other evidence pointing to the fundamental identity of black tongue and pellagra, this association strengthens the probability that the black-tongue preventive and the pellagra preventive, or vitamin P–P, are identical.

## PHYSIOLOGY

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**The Permeability of the Mammalian Erythrocyte to Glycerol and its Bearing on Certain Theories of Cell Permeability.**—M. H. JACOBS (from the Department of Physiology, University of Pennsylvania). The differential permeability of the cell, that is, its tendency to exclude some substances and to admit others with different degrees of readiness, has in the past frequently been explained by one of two theories: the pore theory and the solubility theory. According to the first, the chief

determining factor in cell permeability is the "effective size" of the penetrating molecules; according to the second their solubility in lipoids.

The mammalian erythrocyte shows a behavior with glycerol which appears to be most plausibly explained by the pore theory. Using with suitable precautions the hemolysis method of determining the rate of penetration of this substance, it can be shown that the rate is very different for different species and is affected in a characteristic way by temperature changes, the general, though not the invariable, rule being that in those erythrocytes which are most readily permeable at body temperature the rate of penetration is not greatly retarded by lowering the temperature, while in those which are much less permeable the temperature effect is very great.

As examples of the first condition are the erythrocytes of the mouse and man where the ratio of the penetration rate at one temperature to that at a temperature 10° lower ($Q_{10}$) is in the vicinity of 1.4, which is only slightly higher than that characteristic of a simple diffusion process. At the other extreme are the erythrocytes of the cat, dog, pig and especially of the sheep and ox with $Q_{10}$ values in the vicinity of 3 or greater. The erythrocytes of the rat, rabbit and guinea pig fall in an intermediate class.

It is believed that these differences in the magnitude of $Q_{10}$ are not due to fundamentally different mechanisms of penetration in the different cases but rather to different degrees of modification of ordinary diffusion processes. A relatively simple hypothesis to account for the observed facts is that as the temperature is lowered the pore size is decreased (possibly as the result of increased adsorption). In cases involving small molecules or larger pores, or both, diffusion is little interfered with by lowered temperature but in cases where the pores are small or the molecules are large, or both, the temperature effect is comparatively great.

In support of this view it may be mentioned that for the ox, which of all of the species studied shows the highest $Q_{10}$ value for glycerol, the $Q_{10}$ value for water is that of a simple diffusion process and for the relatively small urea molecule is only a little higher, that is, 1.4. On the other hand, the human erythrocyte which shows for glycerol a $Q_{10}$ value approximately equal to that for urea and not much greater than that for water shows according to Masing a very high one with glucose.

It must be emphasized that the conclusions here stated do not apply to substances which are freely soluble in lipoids and do not necessarily apply to cells other than the erythrocyte which is a highly specialized and in some respects a very peculiar type of cell.

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**Micrurgic Studies on Tissue Culture Cells.**—GEORGE ST. DE RENYI and M. J. HOGUE (from the Department of Anatomy, University of Pennsylvania). The following results were obtained by the authors in studying skeletal muscle fibers from chick embryos of eight to ten days' incubation, cultivated in fluid culture media:

The outgrowing muscle buds represent muscle fibers of a very low grade of differentiation. They do not contain myofibrils, at least it is impossible to show them by optical methods. The buds can be shown to contain only threadlike mitochondria, nuclei, and granules of uncertain nature, in addition to the hyalin sarcoplasma. The surface of the

fibers, even on the delicate growing ends, is covered with sarcolemma. This is firmer than the surface film of other cells. The muscle buds do not become stretched by growth, as Lewis believes. The rapid shortening of the fibers when stimulated mechanically is a real contraction. It has been shown that the sarcoplasma alone is responsible for this contraction, which is not typical, but twitchlike and is not followed by relaxation. No organic connections can be demonstrated between the muscle fibers and the fibroblasts of the culture.

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**The Effect of Iodin and Thyroid Feeding on the Histology of the Thyroid Gland of the Dog.**—W. B. Mosser (from the Department of Surgical Research University of Pennsylvania). Normal adult dogs were fed iodin and dessicated thyroid substance. Iodin ingestion produced an increase in the colloid content of the gland with compression of the cells. Prolonged iodin administration produced a stage of exhaustion in the gland characterized by a loss of architecture and disintegration of the cells. Regeneration of the gland occurs after a rest period. Ingestion of desiccated thyroid substance produced an hypertrophy and hyperplasia of the cells lining the acini.

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**The Mechanism of Ovulation in the Rabbit.**—M. H. Friedman (from the Department of Physiology, University of Pennsylvania). The rabbit differs from other laboratory rodents in that it does not ovulate spontaneously, but only after coitus. Neither artificial insemination nor injections or sperm or semen are successful in provoking ovulation. Yet, ovulation regularly follows coitus with a vasectomized buck and can be produced by rubbing the vulva of a female in heat. Marshall holds the view that the phenomenon is nervous reflex in nature. There has been no decisive work to confirm or to refute this hypothesis. It was with such purpose that these experiments were undertaken.

To test the possibility of intrinsic reflexes from the vagina through the uteri and tubes to the ovaries, it was decided to remove the greater part of the genital tract in the female and note the effect on ovulation. In four rabbits, therefore, both Fallopian tubes and both uteri were removed entirely; leaving behind only that portion of the vagina caudad to the neck of the bladder. Four weeks after operation, these four females were mated. At autopsy three days later, fresh corpora lutea in addition to several corpora hemorrhagica were found in the ovaries of each of these animals. Subsequent histologic examination confirmed these gross findings and showed without question that the removal of the whole genital tract, with the exception of that portion of the vagina between the neck of the bladder and the external orifice, does not prevent ovulation in the rabbit.

As a result of the findings in these experiments, the possibility of an humoral mechanism was more seriously considered. Consequently, a series of ovarian transplants were made, both ovaries being removed at the time of operation, so that the operated animals possessed no ovarian tissues except that transplanted to the rectus muscle. From five to seventeen weeks after the operation, 13 of the 15 animals so prepared accepted coitus as shown by the finding of sperm in the vaginal smear. In each instance, the animal was killed and autopsied about twenty hours after coitus. In 9 of the 13 animals accepting coitus, one or more corpora hemorrhagica were found at the site of the

transplant. Histologic examination of these blood follicles, showed them to be typical corpora hemorrhagica with retained ova. In addition to the corpora hemorrhagica large, unruptured follicles were seen in 7 of the 9 animals and 2 instances genuine fresh corpora lutea were found. In one case, in which 3 corpora hemorrhagica and 2 corpora lutea occurred, the follicles had apparently ruptured into the peritoneal cavity so that no search for the discharged egg was made. In the other instance, however, the follicle had discharged into the surrounding tissues. In several sections ventral to the equator of this discharged follicle, the recently expelled egg was seen. These findings demonstrate clearly that ovulation in the rabbit can occur without the participation of the ovarian nerves, and indicate the presence of some humoral mechanism.

From the recent work of Engle and Smith, and of Zondek and Ascheim, who were able to induce superovulation in the rat by the daily transplantation of the anterior lobe of the hypophysis, came the suggestion that this gland may be involved in the process of ovulation in the rabbit. Following the technique of Engle and Smith, I have transplanted as many as 15 rat pituitaries into a rabbit without provoking ovulation. Due to the almost prohibitive cost of using more glands than this, it was deemed expedient to use a different source of the hormone. On the basis of the recent reports of Zondek and Ascheim which indicate the presence of some substance in the urine of pregnant women, which simulates in action the hormone of the anterior lobe, a series of injection of such urine specimens were made. After the injection of 12-cc. doses of urine from a pregnant woman into a rabbit for four days, large numbers of corpora lutea were found in the ovaries at autopsy. This result was secured using 7 different specimens of urine on 7 rabbits. In one case, the urine was obtained from a woman three months pregnant. Five specimens of urine from nonpregnant women injected similarly gave negative results in 5 rabbits. At present, it is impossible to evaluate these results. They are however, sufficient justification for the undertaking of a statistical investigation to determine whether or not such urine injections may be used for the early diagnosis of pregnancy.

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